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# GUY'S HOSPITAL REPORTS

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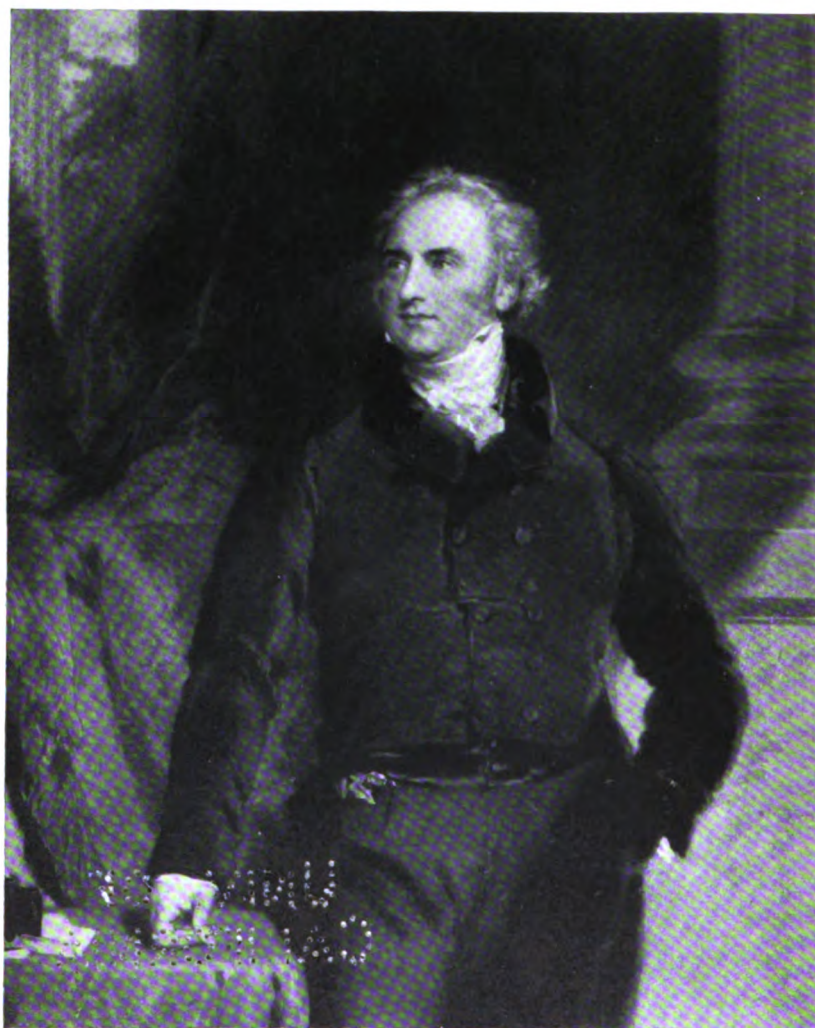
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SIR ASTLEY PASTON COOPER, BART., F.R.S.

The portrait is a reproduction of the well-known engraving by Cousins after the painting by Sir Thomas Lawrence. The original is in the Council Room at the Royal College of Surgeons. It was subscribed for by his pupils in 1814, when Sir Astley was forty-six, but was not completed until some years later.



## ASTLEY COOPER

By SIR CHARTERS J. SYMONDS, K.B.E., C.B., M.S., Consulting  
Surgeon to Guy's Hospital.

### PART I

THE nation cannot know too much of its great men; from their lives we may gather lessons of no small value. In estimating their services we are not to regard merely the direct accession of knowledge which has resulted from their individual labours; we must consider the influence they exerted over the minds of those around them, and the effects of their writings and examples in stimulating others. The life of Astley Cooper affords an example of great industry, of temperance in all things, and of the importance of independent enquiry. He claimed no special gifts; he was certainly not a genius, nor had he the philosophical mind of his contemporary Abernethy. "My own success," he writes, "depended upon my zeal and industry; but for this I take no credit, as it was given to me from above." To what use he put the talent committed to him, it will be the purpose of this sketch to show.

He was born on August 23, 1768, at Brooke, in Norfolk, where his father was rector. When about fourteen, Astley Cooper saved the life of his foster-brother by the timely application of his handkerchief as a tourniquet; he had met with an accident and was bleeding from a wound in the thigh.

He had just completed his sixteenth year when he was sent to London in August 1784, and apprenticed to his uncle, William Cooper. For various reasons he did not reside with his uncle, as apprentices usually did, but instead was placed with Mr. Cline, Surgeon to St. Thomas's Hospital, a circumstance which proved of great importance to the future of the young apprentice. At this time Astley Cooper was a tall, handsome youth, rejoicing in good health, high spirits and a great capacity for enjoyment. For a time he revelled in the attractions of the great city of which he had heard but never before visited. But his sense of duty soon compelled attention to his studies, and here began the wise influence of Mr. Cline. The boy had never expressed any special leaning towards the profession of medicine, so it was quite an open question whether he would take to it or not.

Cline no doubt gauged the tendencies and character of the lad, and set him a task in dissection which put him on his mettle. The performance was successful and the young student seems at once to have grasped the importance of the subject, and from that time became an ardent anatomist. No doubt Cline, as he watched the progress of the dissection which was made in his own house, pointed out the meaning of the structures exposed and directed the young observer to further enquiries.

With Cline lived his mother, a lady of wide intellectual interests with whom Astley spent many hours, and with her and the family he became a great favourite. In the dedication of his work on *Hernia* he gratefully acknowledges his indebtedness to the good influences of Cline's household. Within a short time he was transferred at his own request to Mr. Cline, with whom he continued to live during the seven years of his apprenticeship. This was a change of prime importance when the two surgeons are compared as Masters. Mr. Cooper was a fair anatomist, but as a surgeon rather followed traditional lines, and was too set to take up the newer teaching of Hunter. He indeed said that he never could understand Hunter and usually went asleep at his lectures.

Cline, on the other hand, younger by some years (now aged thirty-eight) was progressive and an ardent admirer of Hunter. Apprenticed at seventeen, he was twenty-four when he attended Hunter's first course of lectures in 1774. He had thus had for seven years one of the older Masters—J. Smith at St. Thomas's, and, as he writes in his second Hunterian oration delivered in 1824, when seventy-four years of age, "I had been for some years in the profession and was tolerably well acquainted with the opinion held by the surgeons most distinguished for their talents then residing in the Metropolis, but having heard Mr. Hunter's lectures on the subject of disease, I found them so far superior to everything I had conceived or heard before, that there seemed no comparison between the great mind of the man who delivered them and all the individuals, whether ancient or modern, who had gone before him."

He was a personal friend of Hunter, and for ten years before Cooper's arrival had imbibed his teaching.

Cline also followed Hunter's experimental methods, and here again led his apprentices onward.

"As a surgeon he was," says Cooper, "cool, safe, judicious and cautious, in anatomy sufficiently informed for teaching and practice. He was a man of great courage. To me he was always kind. He was a great admirer of Hunter, and this high opinion shows his judgment, for almost all of Mr. Hunter's

contemporaries, although they praise him now, abused him while he lived."

While the apprentice was imbibing professional knowledge he was also sharing Cline's democratic opinions, and through him became acquainted with Thelwall. He seems to have taken an active share in the meetings of these men, whose chief object seems to have been to bring about reforms in government, without wishing to copy the French Revolution. It was a time of unrest, for Pitt was struggling with great difficulties both at home and abroad. At home the country was oppressed with taxation, groaned under the effort to fill the army, and revolted against the methods of the press gang, and Ireland, containing one-third of the total population of the British Isles, was openly hostile. The French propaganda had to be met and countered in every direction, and political feeling ran high. Cooper kept up this association for sixteen years, until the time when the vacancy on the staff occurred in 1800. So strong was the feeling that his connection with the democratic party nearly lost him the appointment. The atmosphere surrounding Cline, and in which Cooper lived, must have had its influence, and if it led his apprentices somewhat away from their strict studies, nevertheless must have developed a critical spirit of no small value in directing enquiry into the problems of medicine. It certainly developed a disregard for tradition, and a determination to search for the truth wherever it might lead.

Fortunate also was he in his fellow apprentices. "Johnson," he quaintly says, "was addicted to botany and gave me a taste for instructive pursuits." With Holland and Coleman he attended Hunter's lectures and discussed the subjects as they walked home from Leicester Square to the City, and with the latter he repeated Hunter's experiments and confirmed his conclusions. In all these pursuits there was the guiding hand of his Master, who ever kept alive the scientific side of surgery. Thus we see how fortunate he was in his early surroundings.

While attending Cline's lectures on anatomy and surgery, he, like all pupils, visited the wards at the two hospitals, which were on opposite sides of St. Thomas's Street, but chiefly with his uncle at Guy's. He tells us that he made notes of all important cases seen in the hospitals, attended the post-mortems, examined the parts removed by operation, and, as I have related, conducted experiments to confirm and expand Hunter's teaching. Moreover, he had had the priceless advantage of Cline's personal association, with whom he discussed the cases in the evenings, and under whom he dissected and carried out experiments. At Hunter's lectures he seems to have been a constant attendant

for several years, and there met others of the younger men, who, notwithstanding the obscurity of the style of the great lecturer, recognised the value of the teaching. He brought a vigorous and active mind, free from preconceived notions and the traditions of the older teachers, and was ready to accept the new physiology and pathology. He fixed the principles enunciated by Hunter in his own mind by observation on the living, examination of the dead, and, where necessary, by experiment.

Such then were the opportunities for study offered to an apprentice, and it will be seen that Cooper not only took full advantage of these, but opened out methods for himself.

#### APPRENTICES AND DRESSERS

It will be of interest to digress for a little to refer to the medical education of the time. There were three classes of students. The bulk were the "pupils," those who had been for five years apprenticed to country surgeons, and came up to London aged, roughly, from eighteen to twenty-two. They paid fees, which were divided between the physicians and surgeons.

A limited number of those who could afford the extra fee to the surgeon and the other expenses became "dressers." The apprentices formed another group. These began their studies at the hospital, entering from sixteen to eighteen, and were indentured for seven years. From these the future surgeons were chosen. The fees paid by apprentices and dressers went directly to the surgeon concerned. He was allowed four pupils, who paid a fee divided amongst the members of the staff generally, and four others composed of apprentices and dressers. The latter paid £50 for one year, while the fee paid by the former is not recorded, but it was probably not less than £100 a year.

One dresser was on duty each week, and had to provide entertainment for his colleagues.

Mr. Cooper Forster, for whom the writer "dressed" in 1875, was the last of these dressers, and having ample means he twice held the appointment. When it is remembered that after the morning round he had to provide breakfast at 11 o'clock for all his colleagues, and a supper followed by a guinea bowl of punch, the necessity of means will be understood.

When Cooper began his studies in 1784, the teaching was in general superficial and formal. The lectures in surgery consisted mainly of the relation of cases and followed at the end of the lecture in anatomy. There was little instruction in



pathology, less in physiology, and no scientific basis to the teaching.

There was, however, one surgeon, John Hunter, who had been lecturing for ten years, and had introduced entirely novel views, and these had been accepted by the younger men. It was fortunate for Cooper that his immediate master, Cline, was one of Hunter's most faithful pupils.

### THE HUNTERS

A brief sketch of the rise of the Hunters—William and John—will not be out of place in these *Reports*, as it was a Guy's surgeon who established the school ultimately taken over by John Hunter.

Between Wiseman, the first English surgical writer of any importance, who flourished about 1660, and Cheselden, one of Hunter's teachers, no author of any note had appeared. He wrote a good work on anatomy, and was celebrated for the improvements he introduced into the operation for stone. He took an active interest in the formation of the Company of Surgeons in 1744 and was its first Master. From him Hunter obtained his first lessons in surgery at Chelsea Hospital in 1750, where he continued to operate after leaving St. Thomas's Hospital. He died in 1752. A pupil of Cheselden was Samuel Sharp, who succeeded his preceptor as lecturer at St. Thomas's in 1730, and was from 1733 to 1757 surgeon to Guy's Hospital. He published in 1739 *A Treatise on the Operations of Surgery*, and here showed that the method of treating wounds was beginning to improve. "Matter," he says, "when it is good is no disservice to wounds, and surgeons should therefore be less curious in wiping them clean when they are tender and painful," a direction one had to inculcate by no means unfrequently during the War. Again he says, "A tent brings noxious matter in contact with all parts of the sinus, and makes the case worse." He objects to the use of hot ointments, a relic, no doubt, of the boiling-oil treatment of gunshot wounds of Ambrose Paré's time; he gives directions for better drainage by position and compress, and concludes by cautioning the surgeon "not upon all occasions to search into an abscess with finger and probe, as it often tears them open and indisposes them for a cure." He advocates the use of sutures, and Sharp's "cross stitch" suture for stumps is referred to by Hunter. But the work by which he is better known is the *Critical Enquiry into the Present State of Surgery*, published in 1761. He comments upon the position of surgery,

not only in England, but in France, whither, as a young man, he had resorted for study. He advocates the primary suture of divided tendons, objects to the reduction of a hernia without opening the sac, because, as he very truly says, gangrenous intestine or omentum or irritating fluids may be returned. He moreover recognised that the true cause of strangulation was in the neck of the sac, and not in the external structures; and still more important, he advocates the removal of gangrenous bowel, and the suture of the two ends, by placing one an eighth of an inch within the other. This he says was a suggestion of Cheselden. He criticises adversely the ligature of the sac with a view of preventing recurrence. Referring to the use of the ligature in arresting bleeding in operations, he says, "In all probability it will at last be more generally established, though at present it is not received with the universal acceptance one would wish and expect." He did much to remove the crude notions regarding hydrocele, denying the existence of several reputed forms; and Pott, in his excellent monograph, says, "For a particular elucidation of this subject, the chirurgic world is much obliged to the late Professor Monro, of Edinburgh, and Mr. Samuel Sharp, late of Guy's Hospital, now of Bath." He thus criticises the high operation for stone: "Though the objections have absolutely discredited this way of cutting with the present age, I should not be surprised if hereafter, on particular occasions, it should be revived and practised with success." He further points out, that the most frightful difficulty is the possibility of a contracted bladder; and now that the distension of the bladder can be secured by injection and the use of anæsthetics, the high operation has attained an even more favourable position than he foretold.

Sharp was, as the above extracts will show, a careful surgeon, and was well acquainted with the modern and ancient literature of the subjects he discussed. He was "judicious, a lover of simplicity, and wisely doubtful." "Perhaps," he says, "in this inquisitive age, it may appear surprising that for so long a course of time no one should have detected the falsity of this opinion on hydrocele. But it was the fatality of those days, that physicians and philosophers believed the bounds of science were fixed, and all they studied was how to accommodate their opinions to those of Hippocrates, Aristotle or Galen."

One more extract will show his caution, and his accuracy; commenting on the efficacy of the new remedy—Cortex Peruvianus—in gangrene. "Perhaps," he says, "it seems strange thus to dispute a doctrine established on what is called matter-of-fact, but I will here observe that in the practice of physic

and surgery it is often exceedingly difficult to ascertain a fact."

Sir W. Blizard, in 1815, pays the following tribute to his memory: "Samuel Sharp was an eminent example of industry in the pursuit of knowledge; agreeable to the custom in his day, a consequence of the favourable sentiment generally entertained here of the state of chirurgical knowledge in France, he resorted thither, and became accurately informed in the opinions and operative modes of practice of the distinguished surgeons of that nation."

An almost total absence of pathology is noticeable in Sharp's writings; here and there he discourses upon the cause of disease, and offers an explanation of its course, but, as a rule, he, like all others up to Hunter, was practical only.

A more immediate contemporary of Hunter was Joseph Warner, also one of the surgeons to Guy's Hospital, from 1745 to 1790. In 1784, when sixty-seven, Warner—"the excellent Warner," as one writer calls him—published a valuable and instructive collection of *Cases in Surgery*. His earlier work on the eye went through several editions. The cases are well recorded, and give an excellent idea of the mode of treatment of the time. He advocated and successfully practised the free incision of the chest in empyema, and directs that the knife be kept to the upper margin of the two ribs to avoid the artery. Referring to the translucency of hydrocele, he points out that in young children the hernia sometimes transmits light. He, however, recommends poultices made of the dregs of strong beer, and gives elaborate instructions for the use of ointments. Many of his methods are rough and severe. Still, on the whole, it must be allowed that he added to the advance of the art. Sir W. Blizard says of him, that "the truth of his observations may be depended on, for his motives were pure and honourable."

But the greatest surgeon by far of this period was Percival Pott. In 1751 Hunter joined St. Bartholomew's Hospital, Pott being then thirty-eight and fifteen years his senior. Most of his works were published in Hunter's lifetime, and Hunter refers to these in his surgical lectures. Certainly, a perusal of Pott's essays on head injuries, on hydrocele, and on fractures, impresses one with the great accuracy of his observation, the truth of his deductions, and the wide range of his knowledge. He quotes all the earlier authors, writes in an elegant, graceful style, and indeed must be considered the most polished medical author of the time. He added many new methods of treatment, simplified many others, and was instrumental in removing many of the more rough and harsh methods in vogue.

The earlier Hunterian Orators at the College—Blizard, Abernethy, his pupil Norris, and others—all speak in the warmest praise of Pott. He rose to the highest position in the profession; and when he died, still full of vigour and in active work, at the age of seventy-five in 1788, Hunter was left the first surgeon of the day, being himself now sixty years old.

Blomfield of St. George's, to whom Hunter apprenticed himself to qualify for the surgeoncy, must also be mentioned. "More than any other English surgeon of the time, except Hunter, he might be counted as a scientific surgeon; and whenever he could, he tried to make surgery fit into such physiology as was prevalent in the schools."

One remark applies to all the writings I have referred to, viz. that while there was evidence of the study of morbid anatomy, especially by Pott, there was no pathology in the wide term, no attempt to show that the course of morbid processes was guided by general laws, and few or no principles of treatment.

#### THE EDUCATION OF A SURGEON

For the position of surgeon to a London hospital with a medical school an apprenticeship of seven years to one of the staff was required, and therefore the training depended entirely upon the master. There was no centre outside the hospital to which a student might resort for further instruction, no University supporting men of distinction, no lectures given on the institutes of medicine. Some of the apprentices at the expiration of their time resorted to Paris and other continental schools, where special provision existed to maintain the lectureships. While Cambridge and Oxford enabled London men to take degrees in medicine, the very fact of apprenticeship debarred the surgical pupils complying with the terms of residence, had any desired a university degree.

Examinations in the eighteenth century practically did not exist. A naval surgeoncy, for instance, could be obtained on a minimum of knowledge. The obvious ignorance of such men was a scandal, when one considers the importance of the duties and the valuable lives placed under their care. To improve their knowledge Samuel Sharp started a course of lectures in Windmill Street. This was the first attempt to form a teaching centre outside a hospital, the first extramural school. Anatomy was taught by dissection and demonstration, and surgery as well as might be without the advantages of a hospital. This effort was fortunate in its originator, for Sharp, as mentioned above, was by far the most able surgeon of the day.

Becoming busy in practice, Sharp required an assistant, and found one in a young Scotsman, William Hunter, who had recently come up to London to enlarge his experience, intending to return and work with Cullen.

When Sharp relinquished the lectures in 1747, William Hunter took over the school, which was then a paying concern; the receipts at the opening of his first course amounted to seventy guineas, which he carried away with much satisfaction. Then an assistant was required in the dissecting room, and his brother John, coming up to London on a visit in 1748, was offered the post as soon as he had learned some anatomy himself. Eight years later, during which time he had studied under Cheselden, Pott and Blomfield, he became a partner, and ultimately took over the school and made it famous by his lectures on the "Principles of Surgery."

When John Hunter began these lectures in 1774 at the age of forty-six, it was obvious that a new era had arisen, a new conception of the processes of disease. For the first time surgery was taught as a science, principles were laid down, and comparison made with the natural and morbid phenomena in animals. Unfortunately Hunter was not an attractive lecturer, and hence the class was small, numbering not more than thirty. But the best of the younger men were there, men who took the trouble to listen and discuss amongst themselves the new ideas which he enunciated. Moreover, they found it worth while to attend year by year, for new information was forthcoming as the result of fresh experience and experiment. These lectures continued for nearly twenty years—he died in 1793—and thus many had the opportunity of listening to him, and his influence gradually transformed the teaching in the schools, and from thence in the profession at home and abroad. It must be noted that Hunter refused to publish his lectures, because he felt that he was but on the threshold of knowledge, and that his views must change with increased investigation.

The processes of healing and restoration of injured and of diseased parts were shown to depend on the operation of large and fixed laws. He showed, moreover, that there was a single pathology for medicine and for surgery; that medicine in its widest sense was one and indivisible, and must be studied as a whole, for no part can be understood, if it be studied without reference to the rest of the body. The physician must understand surgery, and the surgeon the medical treatment of disease.

When we remember that in Hunter's time a surgeon was

not supposed to give internal remedies beyond a black draught, the importance of this welding of the two branches of medicine by means of a common pathology will be appreciated.

Amongst those who attended the lectures and have left their impressions and tributes were such men as Cline, who attended the first course, and pays in his oration a warm tribute to the scientific value of the lectures. He sent his apprentices to hear him, and amongst these were Astley Cooper, Abernethy of St. Bartholomew's, whose philosophic mind was well able to grasp Hunter's reasoning and who became the chief exponent of his physiological discoveries, Blizard of the London, Chevalier of the Westminster, Carlisle, Everard Horne, James Earle, all men who have left their mark on surgery and became teachers in the schools.

Thus it will be seen that Cheselden taught Sharp, who became surgeon to the sister hospital established by Thomas Guy, that from Sharp, William Hunter learned surgery and some pathology, for we see from Sharp's writings that he was among the leading thinkers of his time. The methods were passed on to his brother, the famous John, who was to become the greatest biologist and pathologist of the century, and was to revolutionise the teaching of the day, and thence amongst others to the immediate subject of this essay.

#### THE GUY'S HOSPITAL PUPILS' PHYSICAL SOCIETY

One other educative force peculiar to Guy's was the Pupils' Physical Society, founded in 1771. It had been in active operation for fourteen years when Astley Cooper was elected a member on the nomination of his uncle. It was a condition of membership that a paper should be read in the first session of election. This must have been something of an ordeal to a lad not yet seventeen. The subject chosen by Astley Cooper was "Cancer of the Breast," and it is noteworthy that his last publication the year before his death dealt with the same organ. He was frequently fined for non-attendance during his first session. In the following year, however, he became a regular attendant, having recognised the value of discussion, and, as will be seen later, originated another society for the junior men.

#### VISIT TO EDINBURGH

It was provided in Astley Cooper's indentures that he might spend a session in Edinburgh. It is probable that this was a suggestion of Cline's, for his uncle was hardly progressive enough to think of such a move. The date of the visit,

October 1787, was determined by an attack of typhus fever, contracted on visiting a condemned man in Newgate. It so happened that he had known this man in Norfolk, and in his kindness of heart he sought to bring him some comfort.

He had spent three sessions in London and had been a most diligent student under the able guidance of Cline. He was therefore well equipped from his knowledge of anatomy and surgery to take advantage of the experience in a new field. He, moreover, had regularly attended Hunter's lectures, and had had the priceless advantage of discussing the subject of study with his master, Cline, and of repeating Hunter's experiments with his fellow-pupil, Coleman. He says that having heard of the Edinburgh teachers, especially no doubt of Monro, the professor of anatomy, he was desirous of a personal acquaintance. Cooper was now in his twentieth year, and for one so young was well received. He was made a member of the Royal Medical Society—a students' society—and entered actively into the discussions. Here he introduced the novel views of Hunter, and being able to illustrate his remarks from personal observations, made at the bedside and in the dead-house, and also from experiments, he convinced his hearers of the truth of the master's teaching. It is related that he conducted himself with so much discretion and put forward his views in so acceptable a fashion that he won the esteem of his fellow students, an appreciation shown by an invitation to become their President should he repeat his visit.

In later years he wrote an account of this visit with an admirable criticism of the various teachers. He was naturally attracted to Monro, and to him he dedicated, many years later, the second part of his work on Hernia. Of Dr. Gregory he gives a long and sincere appreciation, and says, "that being near them did not diminish the importance I had led to attach to their public character."

His remarks on Cullen are worth repeating: "Never," he says, "shall I forget the veneration with which I viewed Cullen; he was an old man; physic may have much improved since his time, but if Hippocrates was its father, Cullen was its favourite son."

He spent his time visiting and making notes of the cases in the Infirmary as well as attending the lectures. It will be gathered that he was diligent in note-taking all through his course. How interesting it would be to see those notes. I have examined his notes of lectures, and those made in preparing a second edition of the *Handbook of Surgery*, as well as letters to patients and others. The handwriting is difficult to

decipher, but one gathers an impression of the care with which he recorded his observations.

He wrote that one outcome of this visit was that he learned order and system, and formed a plan of investigating cases of disease, which led to the surest and safest method of forming a diagnosis, a plan, he adds, which he pursued all his life to the advantage of his teaching and his practice.

He spent seven months in Edinburgh, and then made a tour in the Highlands on horseback, accompanied by a servant only. Riding back, he spent a little time with friends in the Potteries, enquiring into the industry and the condition of the workers, and, after a short stay in Norfolk, he returned to town in October 1788, "improved in health, professional knowledge and general information, and in seeking the sources from which I had derived most information, Drs. Ash, Gregory and Fyfe seemed especially to claim my gratitude." And then follows a pleasant confession: "Big with my own importance I became presumptuous, but was soon taken down by Newell, Shrapnell and others at the Physical Society."

With Coleman he resumed his attendance at Hunter's lectures, "and this," he says, "was exceedingly improving, as we day by day debated all the way home on his doctrines." And with his companion he "made many experiments, and gained from him an interest in physiological investigation." Coleman rose to be head of the Veterinary College and remained a life-long friend. It was Astley Cooper's privilege to obtain from the King many years later the title of "Royal" for this College.

#### EARLY WORK AT GUY'S AND ST. THOMAS'S

When twenty-one, and in the fifth year of his apprenticeship, he was appointed Demonstrator of Anatomy at St. Thomas's. It must be remembered that there was but a single school at this time, the lectures on anatomy and surgery being given at St. Thomas's and those on medicine at Guy's. For two years he held this appointment, and we hear very little of his work. We know, however, that he continued his investigations in anatomy, and not only in man, but in the lower animals of all kinds, collecting material from the menagerie at the Tower, Leadenhall market, and from the vendors of birds, for it soon became known that there was a market for anything unusual in animal life. Also we gather that he took every opportunity of collecting specimens of morbid anatomy for the museum at St. Thomas's. That he took a keen interest in the all-round instruction of the pupils at this time is further shown in the



foundation of a society confined to the pupils of the two hospitals, where they could discuss the cases amongst themselves. Under another heading it will be recorded that Cooper's first publication appeared in the records of this Society in 1798.

Two years later, in 1791, he was asked by Cline to take a share in the lectures on anatomy and surgery, for which he received £120. He was now twenty-three, and decided to devote the next three years to improving his knowledge, and to teaching, without engaging in practice. This he was enabled to do, as his wife, whom he married the same year, possessed a good income. His father-in-law presented his daughter with a house fully equipped in Jefferies Square, near the Tower, so that Cooper's circumstances were easy. Here he set up a dissecting-room of his own and began work at six o'clock every morning. As apprentice to Cline he was practically assistant, for the apprentices were responsible during the absence of the surgeon, who was only obliged to visit his wards twice a week, though liable to be summoned for emergencies.

In undertaking the lectures he wished to separate surgery from anatomy; to this Cline raised objections, but Cooper convinced his master that both subjects suffered from the method in vogue and he gained his point. The lectures on surgery were given by Cooper three times a week at 8 p.m., those on anatomy, as heretofore, daily at 2.30.

He began by adopting Hunter's plan in dealing with principles first, but was disappointed to find his class inattentive, though he threw into his work all his energy and spared no pains to interest his hearers. He suffered still greater disappointment when the entries for the following session were greatly reduced. It must be remembered that the pupils could take out the lectures under any recognised teacher. Cooper realised that the members of the class had all come from the country, where they had been articled for five years to surgeons taught on the old lines, and could not grasp the newer learning or adapt it to what they had been taught. Such terms as "adhesion," "resolution" and "action" as applied to diseased processes were unknown before Hunter. Cooper in his second course introduced the patients, explained the maladies and injuries, and then applied the physiological and pathological explanation, illustrating the subjects still further by specimens from his museum. The effect was immediate, and the entries for the third course doubled. He attracted larger and larger numbers; at one time as many as four hundred attended his lectures. This method he pursued throughout the forty years of his teaching, enriching his lectures

with examples of cases from his own practice, and as his experience widened, the lectures became more and more valuable. But never did he lose sight of the scientific side, or relapse into the method of earlier lecturers, who dealt with cases only. Always enquiring by dissection, by study of disease in the living and the dead, and by experiment, he was constantly improving his teaching. Many hours of every day were devoted to dissection of normal and diseased structures, not only in man, but in animals. The lessons to be learnt from such vast enquiry were brought to the service of his students. There was always something fresh to bring before them; each year further light was thrown upon old subjects, not from second-hand knowledge, but from the actual work and observation of the teacher himself.

This position as assistant to Cline he held for nine years, during which time he continued to visit the wards with his uncle, and thus was able to give clinical instruction to his class.

He pursued without intermission his studies in anatomy, physiology, comparative anatomy, and in morbid anatomy. He collected and prepared specimens of all kinds, which were added to the museum at St. Thomas's. It was during this period, in 1793, that he was elected to the lectureship in anatomy at Surgeons' Hall. The appointment was renewed in the following year, when he declined a further extension. Though but twenty-five, he drew large audiences, the theatre being crowded, and there was great applause. The demonstrations were given on the bodies of "executed persons," to use his own phrase, and he adds, "I became a very popular lecturer." Cooper thus became known as a brilliant lecturer outside his own school.

When his uncle retired in 1800, Astley Cooper no doubt expected an easy step to the surgeoncy, not because of any relationship, but on account of his long service to the school and to the hospital. But there was opposition of a personal kind. His uncle had become jealous of his success and opposed the appointment, and so did Warner, who, aged as he was, still had influence, and supported Norris, one of the other candidates. But the strongest hostile influence was raised by those who chose to make his old associations with the democrats an objection. Political feeling at the time ran high, we were at war with republican France, and had not recovered from the long struggle with the American colonies. An anonymous letter was received by the Treasurer of Guy's, opposing Cooper's election on political grounds. It was fortunate that some time before this date Cooper and his friend

Coleman had during a walk in Epping Forest decided to withdraw altogether from political associations and devote themselves to their professions. The Treasurer, Mr. Harrison, confident that Astley Cooper was the best of the candidates, sent for him, and pointed out the objection that had been raised. Being convinced of the sincerity of Cooper's change of attitude, he allowed him to canvas the Governors, in whose hands lay the election. Mr. Harrison was right, for Cooper obtained unanimous support, and was appointed surgeon at the age of thirty-two, thereby achieving the height of his ambition. He had made a great reputation as a lecturer, and the school had increased in numbers to the advantage of his colleagues as well as himself; he had been steadily adding to the collection of specimens, and had worked uninterruptedly in his dissecting rooms for nine years. He had made himself so beloved by the pupils and so essential, that I believe something like a riot would have taken place had he not been appointed.

His senior colleagues were Forster and Lucas, neither men of any reputation, and both somewhat lacking in skill and courage. Cooper relates that his first operation was to extricate Forster from difficulties in a lithotomy, and it is recorded that neither of these surgeons would perform operations unless Astley Cooper was present.

He was well equipped for the position. Though he had not performed many operations, he had acquired by his dissections such a knowledge of anatomy as would enable him to operate with accuracy and speed, and from his experiments on animals a refinement of technique not possessed by any of the other competitors. Enquiry by experiment, and the acquisition of dexterity by operating on animals is unfortunately restricted in our country to an extent that has for long checked advance in Surgery. Operations on the dead cannot be compared with those on the living, even if only on one of the lower animals. In the days of Astley Cooper, when anæsthesia was unknown, time was of the essence of success and of mercy, and we shall see how, owing to the dexterity acquired by experiments on animals, he operated with rapidity yet with precision, divided no vessel or nerve unnecessarily, severed the structures without tearing or bruising—in a word inflicted no unnecessary injury. It was said by one of his colleagues that Astley Cooper could operate as well with an oyster knife as another surgeon with the best knife out of Landry's shop. When his seniors were in difficulties, the entrance of Astley Cooper into the theatre dispelled all anxiety, and his help was constantly being sought. He says himself that he and Cline were more useful in extricating

their colleagues from difficulties than in the operations they performed themselves.

#### ASTLEY COOPER AS A TEACHER

Astley Cooper was undoubtedly the most eminent and successful surgical teacher of the day. I have already referred to his methods in teaching, and to the success which attended his efforts. No doubt the popularity of the Borough School was largely due to his personal influence. He was a friend of his pupils, invited their help in his investigations, encouraged questions, and promoted discussions. Besides giving instruction in surgery and pathology, he gave much good advice as to the methods of study.

In the first place he had clear ideas how knowledge should be acquired. He recognised the evil effect of too much teaching, and constantly impressed upon his class the importance of personal observation of the processes of nature. "If," he writes, "the method of observation be not pursued and too much attention be given to theory, they (*i. e.* the students) have afterwards, when they embark on their professional practice, not only everything to learn, but also to abandon those false impressions which hypothesis is sure to create. It is right, therefore, that those who are studying their profession should be aware that there is no short cut to knowledge."

Again he writes : "In collecting evidence upon any medical subject there are but three sources from which we can hope to obtain it—from observation on the living subject, from examination of the dead and from experiments on living animals. By the first we learn the history of disease, by the second its real nature so far as it can be certainly known, and by experiments on living animals we ascertain the processes resorted to by nature for restoring parts which have sustained injuries, and then apply that knowledge to accidents in man."

On another occasion he writes : "It is my duty to state to you my opinion : you must think for yourselves, only do not rest contented with thinking ; make observations and experiments, for without them your thinking will be of little use."

Astley Cooper, like Hunter, urged that there should be no hard-and-fast line between medicine and surgery, that there was a single pathology, and the surgeon should know much of medicine, and conversely the physician of surgery if the best was to result. Nothing can be more true to-day, especially when one sees the practice of medicine, using this term in its widest sense, broken up into so many specialities.

He himself studied physiology in its application to all diseases, and no subject in pathology was neglected. Hence resulted his wide knowledge, his familiarity with disease of all kinds, and in consequence that precision in diagnosis which specially characterised his practice. He constantly urged upon his pupils the importance of the study of morbid anatomy. He recognised that pathology was the basis of medical knowledge, and that each must make the observations for himself, and similarly in the living each case must teach its lesson.

On the value of making notes of observations on all occasions and collecting and classifying these records, he constantly insists. In this connection it is interesting to recall that the teachers of his day invited the pupils to write reports on cases. These were reviewed and commented upon. It is recorded that in one session some eight hundred such reports were presented. Later on reporting was made compulsory and was for long a peculiar feature of the Guy's School. The educative value of these records was recognised by other schools, and the writer recalls a visit from a surgical registrar of another hospital to enquire into our methods with a view to their adoption.

Writing of his friend Coleman, who was head of the Veterinary College, he says, "Whatever a man's pursuit in life, it is knowledge and moral character which give to him his real rank and position, and in proportion as he possesses these, so will he be welcomed in society, respected and beloved.

Writing of his success in life, he says :

"For the benefit of the younger members of my profession let me say, that this success may be always accomplished in a great degree.

"Be kind to every one, and most active to oblige.

"Learn your profession well, be an excellent anatomist, and understand well the practice and duties of your profession.

"Bend the force of your mind to some useful object, and be not multifarious or vacillating in your pursuits.

"Deep science is desirable to the man of fortune—useful science to the physician and surgeon.

"Let your zeal and industry be unbounded."

Astley Cooper was possessed of a fund of humour and was a welcome member of several convivial societies. Moreover, he had a friendly and cheerful way with his pupils, and encouraged them to express their own opinions. But he never hesitated to express his views on intemperance, gaming and the like. Truthfulness in all things he insisted upon.

As President of the College, as well as Examiner, his address to the successful candidates is worth recording here.

"Gentlemen—In the name, and by the authority of the Royal College of Surgeons in London, I admit you members thereof.

"You will have the kindness to sign your names in this book, provided for that purpose, in testimony of the solemn obligation into which you have this day entered.

"And now, gentlemen, give me leave to tell you on what your success in life will depend.

"Firstly, upon a good and constantly increasing knowledge of your profession.

"Secondly, in an industrious discharge of its duties.

"Thirdly, upon the preservation of your moral character.

"Unless you possess the first, Knowledge, you ought not to succeed, and no honest man can wish you success.

"Without the second, Industry, no one will ever succeed;

"And unless you preserve your Moral Character, even if it were possible you could succeed, it would be impossible you could be happy.

"It is with pleasure that I convey to you the wishes of the gentlemen who now surround me, and my own sincere desire that you may be eminently successful in the discharge of your professional duties."

## SPLENIC ANÆMIA AND CHRONIC SPLENOMEGALY

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### I.—INTRODUCTION

It has long been recognised that many chronic infections, such as syphilis and tuberculosis, may give rise to an anæmia of a secondary type, sometimes associated with enlargement of the spleen; but there yet remained a large group of cases in which anæmia and splenomegaly occurred and for which no cause could be found.

In 1866 Gretsels,<sup>1</sup> writing from Griesinger's clinic, described such a case in a child of ten months suffering from an "idiopathic" enlargement of the spleen, severe anæmia, diarrhœa, and slight enlargement of the liver and lymphatic glands, to which he gave the name "splenic anæmia."

Further cases were soon reported, and it was noticed that the proportion of white to red cells in the blood was diminished, and not increased as in leukæmia, so that the term "pseudo-leukæmia" was employed for these cases, following Greisinger, who regarded them as an aleukæmic variety of splenic leukæmia.

The disease did not attract much attention until 1883, when Guido Banti<sup>2</sup> published a paper, in which he assumed that splenic anæmia was the antecedent of his "splenomegaly with cirrhosis," and a further paper in 1894,<sup>3</sup> in which he divided the disease clinically into three stages, passing imperceptibly into one another:—

- (i) the pre-ascitic stage, in which there is an idiopathic splenomegaly, preceding a more or less severe anæmia, and no enlargement of the lymphatic glands; this stage lasts from three to five years or longer;
- (ii) an intermediate stage, characterised by anæmia with a low colour index and leucopenia with a relative increase of lymphocytes, and occasionally slight enlargement of the liver, slight jaundice, diarrhœa and scanty, high-coloured urine. This stage lasts only from one to two years and gradually leads up to

- (iii) the ascitic stage, in which the liver becomes smaller, there is definite ascites and increasing jaundice. The patient becomes emaciated and subject to frequent gastro-intestinal and other hæmorrhages. It is this stage, to which the name Banti's disease is commonly given.

Within a few years of Banti's original description an extensive literature on the subject appeared. A well-defined clinical group seemed to have been identified, and with the methods of pathological investigation then in use there seemed no reason to suppose that all cases of this nature did not have a common cause.

In the light of more recent knowledge, a study of the cases reported by these earlier writers shows that many etiologically very different conditions were included under the term "splenic anæmia."

The first condition to be separated from this group was a form of splenomegaly, having an entirely distinct morbid histology and first described by Gaucher<sup>4</sup> in 1882, who employed the term "*épithéliome primitif*" to the pathological change he found in the spleen and other viscera. Although the actual cause of this disease is not yet known, in view of the peculiar histological features it presents, there is general agreement in placing it in a class by itself, and it is maintained by some authorities (Brill and Mandelbaum)<sup>5</sup> that this disease can, in many cases, be differentiated on clinical grounds.

In 1907 Chauffard discovered a method of estimating the fragility of the red blood corpuscles, and as a consequence the disease "acholuric jaundice" was removed from the splenic anæmia category, and with it disappeared many cases of the familial type of splenic anæmia.

With the introduction of the Wassermann reaction it became possible to differentiate yet another class of case, the syphilitic splenomegalies.

Osler clearly realised that the term splenic anæmia was applied to a clinical condition, which had no specific pathological or etiological basis, when he defined the disease as "an intoxication of unknown nature, characterised by great chronicity, primary progressive enlargement of the spleen which cannot be correlated with any known cause, anæmia of a secondary type, with leucopenia, a marked tendency to hæmorrhage—particularly from the stomach—and in many cases a terminal stage with cirrhosis of the liver and jaundice."

It follows from this very generally accepted definition that



as soon as the cause of a case of splenic anæmia is known, it can no longer be regarded as a case of splenic anæmia. Or, as Mayo tersely says, "Put in the form of an Hibernism, incomplete knowledge is essential to the diagnosis."

In this manner the following forms of splenomegaly have been in turn withdrawn from the symptom group originally called splenic anæmia—Gaucher's disease, acholuric jaundice, the splenomegalies of syphilis, tuberculosis, malaria, kala-azar and von Jaksch's anæmia.

There still remain, however, many cases for which no cause has yet been found, and for which, therefore, according to Osler's definition, the term splenic anæmia is still applicable. The cases to be described here belong for the most part to this latter group.

## II.—THE GUY'S HOSPITAL SERIES OF CASES

During the past twenty years about forty cases diagnosed as splenic anæmia were admitted to the wards of Guy's Hospital. Of these, only those who could be traced or on whom post-mortems were performed are reported here, with the addition of a few in whom the diagnosis seemed fairly certain.

It is to be regretted that in some cases essential details are lacking in the records available, especially among those admitted during the War, when the hospital was suffering from a great shortage of ward-clerks.

Throughout this paper no attempt has been made to distinguish between splenic anæmia and Banti's disease. All cases of splenic anæmia, however prolonged, do not necessarily develop into Banti's third stage with cirrhosis of the liver and ascites, whereas in some the liver appears to be affected comparatively early. The condition of the liver, indeed, would seem to be one of the most variable features in splenic anæmia, and unless extensively damaged it is not possible to determine its exact state clinically.

A study of this series of cases serves to indicate the main features of the disease, and it is therefore unnecessary to describe in detail all the signs and symptoms. Certain features of special interest will alone be discussed.

### *Clinical History and Symptoms.*

The onset is usually insidious. When acute, it must be presumed, in view of the chronic nature of the lesions found in the spleen, that the disease had already been present for some considerable time without causing severe symptoms, and that either an acute exacerbation had occurred or that some inter-current infection had stirred a latent process into activity.

Usually the disease runs a prolonged course; the longest period from the onset of severe symptoms in this series was twelve years in Cases VII and X, sixteen years in Case XX, and twenty-four years in Case III.

All cases do not necessarily proceed to a fatal termination, even if left untreated, and the subsequent history in Cases III, IX, X and XX suggests that in some instance at least the disease is a self-limited process, having an active stage represented by anæmia, indigestion and other symptoms, and a quiescent stage, in which an enlarged, fibrotic and functionless spleen is left as a harmless legacy of past infection.

No age is exempt, but the disease is said to be less common under five years and over fifty-five. In early childhood a difficulty arises as to the relation between splenic anæmia and splenic anæmia infantum or von Jaksch's disease. The latter is characterised by a high leucocytosis with a large proportion of transitional cells, and numerous nucleated red cells; but the distinction is complicated by the fact that a normal infant's blood contains a relatively high number of white cells. Many cases of von Jaksch's disease recover spontaneously, *e. g.* Case IX, possibly for the reasons suggested above. It is impossible in the present state of knowledge to affirm that the adult and infantile forms of splenic anæmia are two separate diseases, and that their distinguishing features are not rather the respective reactions of the adult and the infant to a similar set of causes.

The symptoms may be divided for convenience of description into two groups: (i) those consequent upon the anæmia, such as increasing pallor, breathlessness, palpitations, and lassitude; (ii) those resulting from lesions of the spleen-liver system, such as dragging pains in the abdomen, gastric and other hæmorrhages, and ascites.

The most important and dangerous symptom is hæmatemesis; it may be the first symptom complained of, is usually recurrent, and may be extremely severe. Several pints of blood were vomited in Case XXVI in the course of a few days. The source of this hæmorrhage is not always apparent post-mortem. Dilatation of the splenic vein and œsophageal veins is sometimes found, presumably from torsion produced by the dragging of an enlarged spleen. In other conditions, however, in which the spleen attains an even greater size, as in spleno-medullary leukæmia, copious hæmatemesis is rare. Osler<sup>6</sup> suggests that as the blood flows from the cardiac end of the stomach into the splenic vein, the vasa brevia may become kinked in the gastro-splenic omentum, and as 40 per cent. of the blood from the

stomach flows in this direction, extreme engorgement of the stomach wall would result in oozing. It is possible also that infective material passes from the spleen to the stomach in the form of emboli, giving rise to acute superficial ulceration. In some cases the hæmatemeses are splenic rather than hepatic in origin, as they occur before cirrhosis of the liver has developed and become very rare after splenectomy. In Case XIX a single moderately severe attack of hæmatemesis occurred a few months after splenectomy, and two slight attacks just before his death six years later; in this case, however, a slight degree of cirrhosis was present.

Hæmorrhages from other parts of the body are uncommon with the exception of epistaxis, which, as is seen in this series of case-histories, often occurs quite early in the disease.

The relation of these hæmorrhages to the disease is still not clear. Dr. Lauriston Shaw,<sup>7</sup> writing in these *Reports* in 1902, pointed out that it may be possible to separate cases of splenic anæmia into two broad groups, in which the sequence of events appears to be, in one, (1) large spleen, (2) anæmia, (3) general hæmorrhagic tendency, in the other, (1) large spleen, (2) local gastric hæmorrhage, (3) anæmia.

#### *Morbid Anatomy.*

*The Spleen.*—The spleen, as a rule, is moderately enlarged, rarely attaining the enormous size found in spleno-medullary leukæmia or Gaucher's disease, in which the largest spleens on record have been described. The largest in this series (VI) weighed 2286 grams, compared with the normal of about 200 grams. The spleen from Case XVI was probably somewhat bigger, but the exact weight has not been recorded. The organ retains its normal form; the capsule is generally somewhat thickened and frequently shows patches of perisplenitis on the surface.

In Case XXIV a condition of subacute universal perisplenitis was present, a layer of fibrin being found over the whole of the enlarged spleen; a loud rub had been audible over the spleen for a couple of days, but had become indistinct a few hours before the operation.

Microscopically, the essential feature is the great increase in the amount of fibrous tissue throughout the organ. The splenic veins are frequently thickened and show evidence of endophlebitis. Some of the lymph nodes are apparently healthy, but the majority are sclerosed and replaced by fibrous tissue spreading outwards from the sheath of the follicular artery. Not infrequently the Malpighian bodies are completely re-

placed by dense fibrous tissue. The reticulum of the pulp is usually thickened.

Endothelial proliferation of the venous sinuses of the pulp has frequently been noted, but it does not appear to have been present in any of the cases reported here, with the possible exception of Case XXII. Phagocytosis of red cells is only occasionally seen. Pigment granules are generally found scattered throughout the sections, but are most abundant in the neighbourhood of vessels. Hæmorrhages and infarcts are of frequent occurrence.

The whole picture suggests a defensive reaction to a chronic irritation, and, as the most marked changes are found in the neighbourhood of the vessels and may even involve them, its hæmic origin can hardly be doubted.

*The Liver.*—Cirrhosis of the liver is not confined to those cases presenting the complete Banti syndrome. Slight cirrhosis was seen at operation in several of the present series of cases when its presence had not been established clinically. The post-mortem records give only brief notes, stating that a slight but definite cirrhosis was present, which was chiefly portal in type.

*Portal and Splenic Veins.*—Thrombosis of these veins was found at the autopsy in Cases XIV, XVI, XX, XXIII and XXV of this series, but in all cases it was considered to be a post-operative phenomenon, and too recent\* to have had any part in the causation of the disease. The condition of these vessels is important etiologically in view of two cases published by Dock and Warthin,<sup>8</sup> who described stenosis and calcification of the portal, splenic and mesenteric veins, which they considered to be the primary factor in the causation of the disease in their cases. Other cases have since been recorded, in which chronic obstruction of the portal vein followed an abdominal injury, and in which splenomegaly resulted with secondary anæmia, leucopenia and gastro-intestinal hæmorrhages, presenting a group of symptoms indistinguishable from those of splenic anæmia.

*The Lymph Glands.*—The absence of any enlargement or hypertrophy of the lymph glands is a remarkably constant feature of this disease. No hyperplasia of the hæmolymph glands was noted at the post-mortem examination of any of the above cases. It is possible that the œdema of the neck, chest and arm which occurred in Case XXVI fourteen days after splenectomy, was caused by a compensatory hypertrophy of certain lymph glands causing pressure upon adjacent vessels; but of this there was no proof, and the phenomenon was entirely

unilateral. The x-rays had, however, shown a well-marked shadow in the posterior mediastinum, which was probably due to enlarged mediastinal glands, the pressure of which on the recurrent laryngeal nerve possibly explains the persistent paralysis of the left vocal cord.

*Peritoneum and Gastro-intestinal Tract.*—Chronic peritonitis, generalised, or more frequently local, in the form of perisplenitis and perihepatitis, are constant features of all long-standing cases. Of three patients reported here, who suffered from hæmatemesis and subsequently died, the veins at the cardiac end of the stomach and œsophagus were varicose in one only (Case XXIII). These vessels were found to be considerably enlarged in Case XX, but this patient had never suffered from hæmatemesis.

*The Bone-marrow.*—The bone-marrow of the middle of the femur was examined in Case XVI and found to be abnormally red. No similar observations were made in the other cases. The presence of circumscribed lymphoid areas or myelomata in the bone-marrow, as described by Sir Frederick Taylor<sup>9</sup> and others, was not noted in any of our cases.

### *Pathogenesis*

Whether splenic anæmia and Banti's disease are to be regarded as specific entities or merely as clinical syndromes has been a disputed point for many years. From the fact that the disease can be cured by splenectomy under favourable conditions, it follows that the spleen must be in some way responsible, and that the anæmia, in certain cases at least, must be attributed to the presence of a damaged spleen. The disease must therefore either arise primarily in the spleen, or the enlargement of the latter must be the result of its reaction to some process situated elsewhere in the body.

The morbid histology of the spleens previously described certainly points to some infective agent within the spleen itself. The absence of excessive hæmolysis in this disease is opposed to the view that the splenomegaly is the result of over-action on the part of the spleen in destroying red cells, and also to the view that the anæmia is the result of an hæmolytic process. That some substance manufactured in an infected spleen exerts a repressive action on the hæmopoietic functions of the bone-marrow would seem to offer a more likely explanation of the anæmia in this disease. It may be objected that such cases as those described by Dock and Warthin had their origin in a lesion situated at first outside the spleen; but these writers themselves admit that the process may have been in the reverse direction. Banti observed an endophlebitis with

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calcification of the splenic veins, extending up to, and even into, the portal vein.

With the single exception of acholuric jaundice, all those conditions which have now been removed from the splenic anæmia group have been shown to be of protozoal or bacterial origin. The demonstration of an infecting agent in the remaining cases would therefore seem to offer the most hopeful field for future research.

### *The Demonstration of Infecting Organisms in the Spleen*

Banti attempted to demonstrate micro-organisms in the blood and viscera in splenic anæmia, and also to reproduce the condition in lower animals, but without success. In spite of this, he insisted that the splenic enlargement was primary and due to an unknown infective agent in the spleen.

In 1914 A. G. Gibson,<sup>10</sup> of Oxford, reported the finding of a streptothrix in certain cases resembling Banti's disease; cultural confirmation was not then possible, but has since been achieved. Five cases were reported in full; the first had tuberculosis of the lungs and liver with splenomegaly; the second was Case XIX of this series; the third a case of mediastino-pericarditis with enlarged spleen; the fourth a case of chronic heart failure without splenomegaly; and the fifth a case of phthisis with a syphilitic liver and splenomegaly.

It is difficult to understand the exact part played by this organism in such diverse conditions as the above, and its relationship to Banti's disease is not yet clear, but it may well prove to be a causal factor in some cases. Further results of Gibson's work will be awaited with interest.

Hollins<sup>11</sup> in 1915 succeeded in producing splenomegaly with secondary anæmia in rabbits by repeated subcutaneous injections of *Bacillus coli*. At autopsy, however, he was unable to recover any living micro-organisms.

### *Syphilis and Splenic Anæmia*

Gibson's second case, referred to above, was quoted by Osler as an example of a syphilitic splenomegaly simulating splenic anæmia. Since the introduction of the Wassermann test a certain number of cases of splenic anæmia have been found to give positive reactions, and this has led to much dispute as to whether these cases are syphilitic in origin or whether the lesions in splenic anæmia are such as will sometimes give a positive result with this test, just as, according to certain French authors, many cases of ordinary cirrhosis of

the liver give a positive Wassermann reaction, presumably in the absence of syphilitic infection. Possibly, also, splenic anæmia may occur in a syphilitic subject, as an independent affection, as may have been the case in No. XXIV of this series.

In any case it has been definitely established that syphilis may give rise to a clinical picture indistinguishable from splenic anæmia, and that we are therefore justified in relegating such cases to a class by themselves, for which "syphilitic splenic anæmia" may be a convenient title. Such a condition was described by Coupland<sup>12</sup> in 1896, in a woman whose spleen was removed with great benefit for what was thought to be simple splenic anæmia, and who died two years later from gastro-intestinal hæmorrhages and ascites, and in whom the liver was found at autopsy to be syphilitic.

W. J. Mayo<sup>13</sup> has recently removed the spleens from five patients with chronic syphilitic splenomegaly, who had resisted all anti-syphilitic treatment; after splenectomy the anæmia disappeared, and all the patients reacted favourably to very mild anti-specific measures. In two of these cases the *Spirochaeta pallida* was subsequently recovered from the spleens.

It is the familiar experience of those who have had charge of venereal clinics that, so far as the Wassermann reaction is concerned, certain cases resist all treatment, however active and prolonged. The assumption is that the spirochæte or its products is in some manner locked up in the tissues and cannot be reached by any ordinary method of treatment. Such an hypothesis would account for the improvement which immediately follows removal of the spleen in the type of case under consideration, and for the disappearance of the positive Wassermann reaction in Case XIX without further anti-syphilitic remedies being used.

#### *Focal Sepsis and Splenic Anæmia*

The striking sequence of events in Case VI justifies the belief that the disease was secondary to focal infection. Three years after the complete eradication of an obvious focus of infection in the teeth, both the anæmia and the enlarged spleen had disappeared. It is possible that the tonsils were acting in a similar manner as a primary focus of infection in Case IX.

It is not very uncommon to find women with uterine fibroids, which give rise to constant loss of small quantities of blood, and in whom there is a slight but definite enlargement of the spleen. Repeated loss of small quantities of blood produce a severe secondary anæmia, but do not cause enlargement of the spleen unless some other factor is present as well. In one

such case recently in Guy's Hospital, Mr. C. H. Medlock observed that both the anæmia and the enlargement of the spleen disappeared shortly after the uterus had been removed. The most probable explanation is that the uterus was acting as a focus of infection, from which organisms were being carried to the spleen, which had become enlarged in its efforts to deal with them, and that the whole process was cut short by the removal of the focus of infection.

It is not suggested that this case is a typical example of splenic anæmia due to a focal infection; it is only recorded to show the possible relation between a focal infection and disease of the spleen. A similar cause operating over an interval of many years would seem to offer a reasonable explanation of Case III of this series.

#### *Tuberculosis and Splenic Anæmia*

Massive tuberculosis of the spleen causing great enlargement, a secondary type of anæmia and no obvious evidence of infection elsewhere, is rare. Giffin,<sup>14</sup> however, states that it is not exceedingly rare, but that it is probably always secondary to a primary focus in some other part of the body. Winternitz<sup>15</sup> in 1912 collected fifty cases of this type, and of those operated upon 59 per cent. recovered; in the remaining cases the disease ultimately became generalised and proved fatal.

Secondary tuberculosis of the spleen is quite common and usually miliary in type. Case XVIII was perhaps of this nature.

A consideration of the evidence afforded by a study of these cases, defective as it is in many instances, leads to the conclusion that in splenic anæmia we are dealing with a clinical entity—a syndrome resulting from fibrosis of the spleen, in whatever manner this was originally produced. The anæmia, when not directly caused by hæmorrhages, is probably due to a depression of the normal bone-marrow functions caused by circulating toxins manufactured in the infected spleen, rather than to an excessive blood destruction occurring in the spleen.

Seeing that a large number of cases can be cured by removal of the fibrotic spleen, it might be thought that the demonstration of the specific infective agent at work in any case would be of no practical value. But such knowledge may well have an important bearing upon the prognosis, and the operative mortality may be still further reduced by a more scientific selection of cases. It is possible also that only the toxins of certain organisms give rise to cirrhosis of the liver, thus accounting for the fact that some cases never develop the complete



Banti syndrome, however long the patient may live after the spleen becomes infected.

#### TREATMENT

A search for and removal of possible foci of infection should never be omitted; if after a reasonable time no improvement follows, the question of splenectomy has to be considered. If a positive Wassermann reaction be obtained, ordinary anti-syphilitic remedies should be given, but the treatment should not be prolonged if no improvement occurs, as in many of these cases early operation appears to offer the best hope of a cure.

In the majority of all cases removal of the spleen is the only possible method of treatment. The operative mortality in the present series of cases is exceedingly high; but a reference to the case-histories shows that in most of the fatal cases operation was attempted as a last resort in patients who were *in extremis*, and who had suffered from the disease for many years. Of seven cases under the age of twenty-five in whom the spleen was removed, five made a complete recovery; one of these died a year later from an independent infection, and another, Case XIX, died six and a half years later. The importance of operating as early as possible in the course of the disease is thus well illustrated.

Dr. A. F. Hurst lays special stress on the importance of realising that the presence of a rub over the spleen is an urgent indication for operation. The condition found on opening the abdomen in Case XXIV clearly showed that if there had been any delay the spleen would have become so universally adherent to the surrounding parts that excision would have been impossible. On the other hand, even the presence of definite cirrhosis with well-marked ascites and severe anæmia is no contra-indication, especially if transfusion be given intravenously, as shown by the recovery of Case XXVI, in which the condition prior to operation was extremely critical. Incidentally it may be noted that in this latter case there was no recurrence of the ascites after the operation. Dr. A. F. Hurst has put forward the view that the probable explanation for this is that the portal vessels are capable of dealing with a normal quantity of blood, but are overwhelmed when they also receive the enormous additional quantity supplied by the large spleen, and consequently they become incompetent.

Two Cases, XIX and XXI, are alive and well six and a half and six years respectively after splenectomy.\* Cases XXII,

\* Case XIX died in November 1921. *Vide* detailed report.

XXIV and XXVI are also well five years, two years, and eighteen months respectively after operation.

It would be unfair to draw conclusions as to the operative mortality in splenic anæmia from such a small number of cases. Moynihan<sup>16</sup> quotes the figures from the Mayo Clinic, where, up to September 1920, seventy-three operations had been performed with nine deaths, an operative mortality of 12·3 per cent.

X-ray applications were tried in several of our cases, but without success, with one exception. A temporary reduction in the size of the spleen could generally be produced, and as a preliminary to splenectomy this may be of service. The one exception is Case III (*vide* detailed report), in which x-ray applications over the region of the spleen were the only treatment employed. This patient is now, sixteen years later, a comparatively healthy woman.

The value of blood transfusion can hardly be over-estimated, either as a means of restoring a very anæmic patient to a condition in which operation can be performed without undue risk, or as a method of resuscitation during an extensive and formidable operation, in which much loss of blood is liable to occur. The striking manner in which both these points were illustrated in Case XXVI has been referred to previously. In this connection, a further suggestion made by Dr. A. F. Hurst may be mentioned. During the operation, if the anæmia is severe, a considerable quantity of blood could be saved if the splenic artery were ligatured first and the spleen squeezed before the vein were tied, as the spleen contains an enormous quantity of blood, which could in this way be saved for the patient.

#### CONCLUSIONS

1. Splenic anæmia is not a specific disease, but a clinical syndrome produced by a variety of causes.
2. This syndrome is probably always the result of a chronic infection situated in the spleen itself.
3. In some cases a primary focus of infection can be discovered elsewhere in the body, and the removal of such a focus will cure the disease.
4. All cases do not necessarily proceed to a fatal termination, however prolonged. In some the process is self-limited, the active infection of the spleen dies out or is overcome, and spontaneous cure results.

In conclusion I wish to offer my thanks to the members of the consulting and active staffs for their kindness in allowing me to publish details of the cases formerly under their care.

I wish also to thank Dr. A. F. Hurst for his advice and assistance, and Dr. A. G. Gibson for giving me the benefit of his experience, and allowing me to see the results of much of his yet unpublished work.\* I am indebted also to Dr. Skene Keith for kindly performing the Wassermann reactions in the cases which I was able to trace.

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## CASE HISTORIES

The following cases are described in full, as they illustrate important points in connection with pathology, symptoms, prognosis or treatment of splenic anæmia.

*Case III.—Splenic Anæmia: good health after twenty-five years with splenomegaly, anæmia and leucopenia.*

Harriet H., *æt.* 43, married, with two children, was admitted under Dr. Horrocks on December 20, 1900. Three or four years before she had noticed a lump in the left side of her abdomen, but this caused no inconvenience. A year ago her menses became more frequent, and more profuse.

On admission she appeared to be a fairly well-nourished, healthy-looking woman. The spleen was enormously enlarged, the lower edge reaching to within an inch of the anterior superior spine, the anterior border an inch to the right of the umbilicus; it was firm to the touch. The liver was not enlarged. There was no ascites.

\* Since writing the above, Dr. Gibson has published some further results of his work in the Schorstein Lecture, *Lancet*, October 29, 1921.

A blood examination showed—

Red cells, 3,600,000 per c.mm.

White cells, no leucocytosis.

She was discharged a week later with her condition unchanged, a diagnosis of splenic anæmia having been made.

During 1901 and 1902 she always lost a large quantity of blood both at and between her menses, and she suffered from bleeding hæmorrhoids. She had never vomited blood or suffered from epistaxis. She had struggled on with her housework throughout this period, her chief trouble being the dragging pain caused by the lump in her abdomen.

She was readmitted under Dr. Taylor on February 11, 1905. There was a decided yellow tinge about the face, and the sclerotics were also yellow. The size of the spleen was unaltered. The liver was still not palpable, and there was no ascites.

A blood examination showed—

Hæmoglobin, 50 per cent.

Red cells, 3,600,000 per c.mm.

White cells, 7,500 per c.mm.

X-rays were applied over the region of the spleen on alternate days for a period of two months with intermissions, beginning on April 4, and by May 2 the spleen was considerably reduced in size, the lower border now being at the level of the umbilicus. No further reduction in size occurred, but an x-ray burn developed on the lower part of the abdominal wall and treatment was therefore discontinued.

Blood counts were made throughout this period but were complicated by the fact that she was losing blood per rectum almost daily.

A blood count on June 13 showed—

Hæmoglobin, 40 per cent.

Red cells, 2,750,000 per c.mm.

White cells, 5,600 per c.mm.

In response to the general and local measures adopted the amount and frequency of the hæmorrhages became considerably diminished, but they were never completely controlled. She has been attending the out-patient department at monthly intervals since her discharge in 1906 until now, September 1921, at first under Dr. A. F. Hurst, and since 1915 under Dr. G. H. Hunt.

During this period she has been able to do light household work, but she has continued to lose blood in small quantities per rectum almost daily, but only occasionally per vaginam. At intervals she is troubled with a dull pain in the left side of the abdomen, but the enlarged spleen causes her very little inconvenience.

When seen in April 1921 she was a healthy looking woman, young for her age (64 years), well covered, with a fresh complexion

and red lips. She did not appear to be at all anæmic. On examination, the spleen was enlarged and tender, and did not feel very hard; the lower border was at the level of the umbilicus, and the anterior border reached the mid-line. The liver was not enlarged and there was no ascites.

A blood count showed—

Hæmoglobin, 78 per cent.

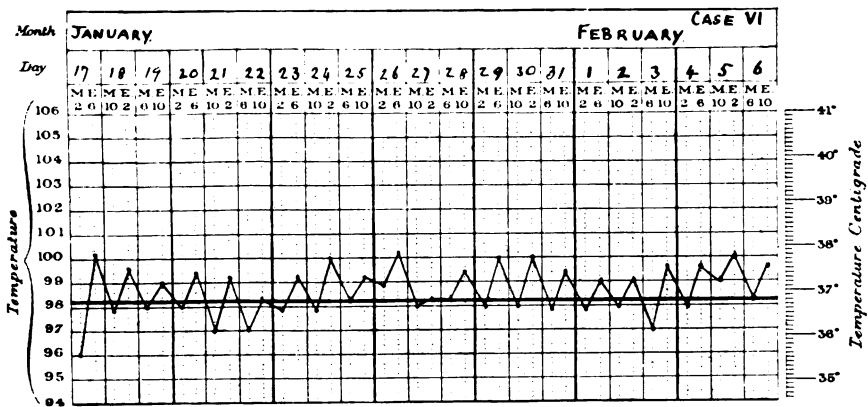
Red cells, 3,490,000 per c.mm.

White cells, 3,940 per c.mm.

A blood film showed no abnormality, and the Wassermann reaction was negative.

*Case VI.—Splenic Anæmia associated with oral sepsis. No splenectomy. Perfectly well sixteen years later.*

Elizabeth L., æt. 47, was admitted under Dr. Newton Pitt on January 17, 1905, for pain in the left side of the abdomen.



About three months previous to admission she accidentally noticed a hard lump in the left side of her abdomen, and she occasionally had a feeling of fullness after meals.

Three weeks before admission she was seized with a severe pain in the left side; the pain recurred at intervals, had no relation to meals, and was made worse by standing or walking. Lately she had suffered from attacks of epistaxis.

On admission her teeth were in a very septic condition. The spleen was greatly enlarged, the lower edge being felt five inches below the umbilicus, and the anterior edge in the mid-line. The liver was not palpable. No free fluid could be detected in the abdomen.

A blood count showed—

Red cells, 3,540,000 per c.mm.

White cells, 4,400 per c.mm.

There was an irregular pyrexia throughout her stay in hospital, as shown in the chart.

Splenic anæmia was diagnosed by Dr. Pitt, who expressed the opinion that the whole condition might be due to the septic teeth acting as a focus of infection.

All her teeth were subsequently removed. She continued to have attacks of epistaxis; and she still ran a slight temperature. On February 9, 1905, she was discharged, her general condition and blood count being almost unchanged.

Three years later she was examined by her doctor, who was unable to find any trace of an enlarged spleen.

From that time until now she has been in excellent health, and has been able to get about and do ordinary housework. She was recently (sixteen years after leaving Guy's) examined by Dr. W. P. Morgan of Seaford, who kindly wrote that she was in excellent health, and that her spleen was not palpable.

The subsequent history of this case shows that Dr. Pitt's suggestion as to the septic origin of the splenic anæmia in this case was probably correct.

*Case VII.—Mild, chronic Splenic Anæmia of thirteen years' duration.*

Annie P., *æt.* 7, was admitted under Dr. Hurst on April 29, 1908.

A week before she was suddenly seized with pain in the abdomen whilst skipping, and vomited about a pint of blood. She remained in bed for a week without further symptoms and was then sent up to the hospital.

A blood examination on admission showed—

Hæmoglobin, 58 per cent.

Red cells, 2,900,000 per c.mm.

White cells, 3,200 per c.mm.

The lower border of the spleen reached to about three inches below the umbilicus. The liver was not enlarged, and there was no enlargement of lymph glands.

Splenic anæmia was diagnosed, but as she had had no return of symptoms and her blood count had returned to normal, the question of splenectomy was dismissed and she was discharged on June 3.

She remained in indifferent health for the next five and a half years, occasionally suffering from slight epistaxis, and attacks of abdominal pain, but did not again vomit blood. She was re-admitted on November 6, 1913, after four days illness of headache, abdominal pain, and vomiting, without hæmatemesis. The spleen was tender, the lower border reaching one inch below the umbilicus. The liver was not palpable. The Wassermann reaction was negative.

A blood count showed—

Red Cells, 5,230,000 per c.mm.

White Cells, 12,000 per c.mm.

The acute symptoms rapidly subsided and she was discharged. She was again admitted on July 9, 1914, with a similar attack of headache, abdominal pain and vomiting, but no hæmatemesis. The spleen was tender, the lower border reaching the level of the umbilicus. The liver was not palpable. The Wassermann reaction was again negative.

A blood count showed—

Hæmoglobin, 50 per cent.  
Red Cells, 2,400,000 per c.mm.  
White Cells, 4,270 per c.mm.

A further blood count taken three weeks later showed—

Hæmoglobin, 75 per cent.  
Red Cells, 4,800,000 per c.mm.  
White Cells, 3,600 per c.mm.

The acute symptoms again rapidly cleared up and she was discharged.

When seen in April 1921, exactly thirteen years after her only hæmatemesis, she stated that she still occasionally suffered from abdominal pain, and that the lump in her side was very tender. She had been able to do light work, and had now been married one year. She had never vomited blood since the first attack in 1908. She occasionally had slight bleeding from the nose.

She is a pale, undersized-looking girl of 20 years. On examination the spleen was found to be enlarged and tender, but did not feel particularly hard, the lower border reached the level of the umbilicus, and the anterior border the mid-line. The liver was not palpable, and there was no evidence of ascites, and no enlargement of lymph glands.

A blood count showed—

Hæmoglobin, 80 per cent.  
Red Cells, 3,600,000 per c.mm.  
White Cells, 3,100 per c.mm.

The Wassermann reaction was negative.

*Case IX.—Splenic Anæmia associated with tonsillitis. No splenectomy; quite well eight years later.*

George C., æt. 6½ years, was admitted under Dr. Newton Pitt on June 2, 1913, for enlargement of the spleen and vomiting.

At four years of age he had his tonsils cut, not enucleated. A fortnight previous to admission he began to be sick in the mornings, generally after breakfast, and it was then noticed that his abdomen was getting larger. He never vomited blood, and his appetite remained good.

He frequently complained of feeling tired. On admission his temperature was 101·8°, pulse 136, and respirations 36. He looked anæmic, and his face had a pale yellow tinge, but

there was no jaundice. The tonsils were acutely inflamed. The spleen was greatly enlarged, the lower border reaching to the anterior superior spine. It was not tender, but a well-marked rub could be heard over it. The edge of the liver was felt just above the level of the umbilicus. There was no ascites.

A blood count showed—

Hæmoglobin, 70 per cent.

Red Cells, 2,980,000 per c.mm.

White Cells, 6,000 per c.mm.

The Wassermann reaction was negative.

Dr. Newton Pitt suggested a diagnosis of either von Jaksch's anæmia or splenic anæmia. The acute symptoms due to the tonsillitis subsided, and he was discharged on August 22, the spleen and blood picture remaining in much the same condition.

When seen early this year (1921) he stated that he had been quite well since his discharge eight years previously. He had had no further trouble with his throat, but had had his tonsils "done again." He looked extremely fit, and neither the spleen nor liver was palpable.

A blood count showed—

Hæmoglobin, 87 per cent.

Red Cells, 4,320,000 per c.mm.

White Cells, 7,480 per c.mm.

The Wassermann reaction was negative.

*Case X.—Splenic Anæmia. No splenectomy; quite well twelve years later.*

Elizabeth J., *act.* 44, was admitted under Dr. Fawcett on April 24, 1914, for vomiting blood.

During her fourth pregnancy, in 1909, she suddenly vomited a considerable quantity of blood, but soon recovered, and the pregnancy terminated normally. No further trouble was experienced until early in 1914 her appetite began to fail. She vomited blood on two occasions between January and April 1914. The spleen and liver were both enlarged.

A blood count showed—

Hæmoglobin, 60 per cent.

Red Cells, 2,800,000 per c.mm.

White Cells, 3,800 per c.mm.

The Wassermann reaction was negative. There was no pyrexia throughout.

At the end of a month's treatment with arsenic, the red cells had increased to 5,330,000 per c.mm., but no change was found in the condition of the spleen and liver. The patient, however, felt very much better, and was discharged. She has had no return of the symptoms and has enjoyed very good health.



When seen early this year, she looked a healthy woman. The lower border of the spleen was felt three fingers' breadth below the costal margin; it was hard and the edge felt irregular. The lower border of the liver reached two fingers' breadth below the costal margin, but it was not very hard.

A blood count showed—

Hæmoglobin, 84 per cent.  
Red Cells, 5,200,000 per c.mm.  
White Cells, 8,600 per c.mm.

The Wassermann reaction was negative.

*Case XIX.—Splenic Anæmia with positive Wassermann reaction; no response to anti-specific treatment; apparent complete recovery with negative Wassermann reaction after splenectomy, but death from acute illness with cerebral symptoms and hæmatemesis six and a half years later.*

Henry S., when *act.* 12 in August 1913, had severe hæmatemesis and melæna which continued for thirty-six hours. When first seen by Dr. A. F. Hurst, in September 1913, his spleen was very large, and the liver hard and slightly enlarged.

A blood count showed—

Hæmoglobin, 36 per cent.  
Red Cells, 2,200,000 per c.mm.  
White Cells, 4,050 per c.mm.

The Wassermann reaction was positive. There was no enlargement of lymphatic glands, and clinically he was a typical case of splenic anæmia.

He was vigorously treated with salvarsan, mercury and iodides. The Wassermann reaction became only temporarily negative, and there was no great improvement in his condition; a severe hæmatemesis occurred in January and February 1914, and again in January 1915.

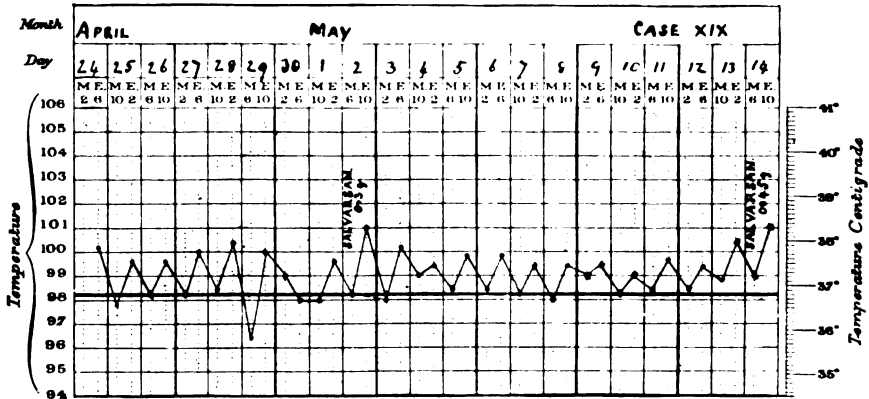
Although operation was advised by Dr. Hurst when the patient was first seen, this was not performed until March 10, 1915, when Mr. R. P. Rowlands removed the spleen. At the operation the liver was seen to be definitely cirrhotic. There was no ascites.

Microscopically the capsule of the spleen was not greatly thickened. Immediately beneath the capsule were many recent hæmorrhages, and scattered throughout the section were numerous pigment granules, not in any obvious relation to the vessels. There was no great excess of fibrous tissue anywhere and no marked endothelial proliferation. The Malpighian corpuscles, though few in number, appeared normal. The vessels everywhere looked quite healthy.

Rapid improvement occurred after the operation. The Wassermann reaction, which was positive immediately before operation, became negative directly afterwards, and is still

negative (January and June 1921), although no further anti-syphilitic treatment was given.

There was throughout a low irregular pyrexia (Chart I), which subsided a few weeks after operation; a slight rise in temperature followed immediately after each dose of salvarsan.



When seen in January 1921, he was a fairly healthy-looking youth, though somewhat undersized. He stated that, with the exception of a small hæmatemesis in 1918, he had enjoyed perfect health since the operation, and for the last two years had been working as a clerk in the City. The liver was not palpable.

CHART II.  
SUMMARY OF BLOOD-COUNTS, ETC.

Date.	Hb. %	Red Cells per c.mm.	White Cells per c.mm.	Treatment.	Clinical condition.
Sept. 26, 1913	36	2,200,000	4700	Nil	Wassermann +
Nov. 11, 1913	58	3,300,000	4050	"	"
April 17, 1914	30	2,550,000	—	Salvarsan, Hg. and Pot. Iod.	"
May 4, 1914	38	2,630,000	—	"	Liver less easily palpable. Spleen as before. Was- sermann +
May 7, 1914	44	2,600,000	—	"	Liver half inch smaller. Spleen definitely smaller.
May 20, 1914	50	3,450,000	—	"	Spleen increasing a little.
June 12, 1914	80	4,120,000	—	"	Spleen shows no change.
Sept. 29, 1914 (after 3 months in hospital)	70	5,200,000	1760	"	Wassermann — No change.
Jan. 29, 1915	50	3,230,000	2320	"	No change in liver and spleen. Wassermann +
March 9, 1915	40	3,260,000	1560	Operation No anti- syphilitic treatment	Wassermann negative.
March 24, 1915	50	4,070,000	9160		
April 9, 1915	50	4,700,000	9375		"
Sept. 23, 1915	89	4,800,000	5000		
Sept. 15, 1919	86	4,920,000	5040		
Jan. 1921	100	4,560,000	5100		

For the following notes as to his subsequent history I am indebted to Dr. E. J. F. Hardenberg, of Chingford.

He had been quite well and entirely free from symptoms up to November 27, 1921, when he complained of severe pain in the right side of the face. The pain was neuralgic in type and later spread to the back of the head and neck.

On the following day his temperature rose to 101° F., and he vomited a considerable quantity of darkly stained material. There was slight neck rigidity. A little later he had an epileptiform convulsion, the pupils reacted sluggishly to light, the knee-jerks were brisk, and the plantar reflexes were both flexor. He remained semi-conscious. He had two small hæmatemeses, and his motions became black. The next day he had another fit and died, four days after the onset of acute symptoms. Unfortunately permission for a post-mortem examination was refused, and therefore it is impossible to say to what extent this terminal illness was connected with the splenic anæmia.

*Case XXIV.—Splenic Anæmia in a Syphilitic Youth: acute perisplenitis with rub audible over the spleen; splenectomy; recovery.*

William McK., æt. 22, was admitted under Dr. A. F. Hurst on August 29, 1919, for anæmia and enlargement of the spleen. His mother and father were said to be quite healthy. He was their only living child, his mother having three miscarriages after he was born. He is said to have had two attacks of measles, the first leaving him almost blind, and the second causing almost complete deafness.

Three months before admission he first noticed a swelling in the left hypochondriac region, and about the same time he began to lose weight.

On admission he was a feeble-looking, pale youth, with well-marked interstitial keratitis of both eyes, and he was very deaf. The lower border of his liver was felt two fingers' breadth below the costal margin, and was very hard. The spleen reached just below the umbilicus, and a loud rub could be heard and felt over it. A small quantity of free fluid was present in the abdomen.

A blood count by Dr. G. W. Nicholson showed—

Hæmoglobin, 64 per cent.

Red Cells, 4,040,000 per c.mm.

White Cells, 7,160 per c.mm.

The Wassermann reaction was positive.

Splenic anæmia was diagnosed, and it was decided to operate at once, before trying the effect of anti-syphilitic treatment, as, in view of the rub over the spleen, it was realised that any delay might make operation impossible, owing to the development of perisplenic adhesions. On September 8, 1919, Mr.

L. Bromley removed the spleen. The patient made an uneventful recovery. The liver appeared to be normal.

On October 21, six weeks after the operation, a blood count by Dr. Nicholson showed—

Hæmoglobin, 64 per cent.  
Red Cells, 4,890,000 per c.mm.  
White Cells, 12,680 per c.mm.

Differential count—

Polymorphs, 42·2 per cent.  
Lymphocytes, 32·3 per cent.  
Eosinophils, 9·2 per cent.  
Hyalines, 15·2 per cent.  
Basophils, 1·2 per cent.

The Wassermann reaction was still strongly positive.

In view of the very great improvement in his general condition, it was considered unnecessary for the present to give active anti-syphilitic treatment, and the patient was discharged, to attend as an out-patient.

When seen early in the present year (1921) he was extremely pleased with himself, and said that he had not had another day's illness and that the operation had made a new man of him.

A blood count showed—

Hæmoglobin, 75 per cent.  
Red Cells, 5,190,000 per c.mm.  
White Cells, 13,300 per c.mm.

The Wassermann reaction was strongly positive.

*Case XXVI.—Splenic Anæmia with cirrhosis of liver and ascites.  
Complete recovery after splenectomy.*

Elvin B., æt. 14, was admitted under Dr. A. F. Hurst on February 16, 1920, for hæmatemesis. A few years ago he had frequent attacks of epistaxis, and two months before admission his gums had bled. He was supposed to have always bruised easily. On February 13, 1920, he returned from work with a headache, and in the evening vomited an ounce of blood. Shortly afterwards he vomited half a pint of blood, and then became very faint and pale. Early next morning he vomited a further half-pint of blood, and it was then noticed that his face and chest were covered with purpuric spots.

On admission he was very drowsy, with pulse 120 and temperature normal; his face was very pale. The skin, especially over the neck and chest, was covered with minute purpuric spots, whilst below the left eye and on both shins were larger purplish areas.

Enlarged glands were present on both sides of the neck, and in the axillæ and groins. The lower border of the spleen was felt at the level of the umbilicus; the liver was not palpable, and there was no evidence of ascites.

A blood count showed—

Hæmoglobin, 55 per cent.  
Red Cells, 3,660,000 per c.mm.  
White Cells, 6,200 per c.mm.

Clotting time was 1' 45".

The Wassermann reaction was negative.

On the evening of admission he vomited a pint of blood and a similar quantity the next day. By this time the purpuric rash had begun to fade.

On February 22 a large swelling appeared in the middle of the left thigh on the anterior surface, which was considered to be a subperiosteal hæmatoma. In the course of a few days the swelling disappeared without active interference.

A blood count at this time showed—

Hæmoglobin, 22 per cent.  
Red Cells, 2,280,000 per c.mm.  
White Cells, 4,200 per c.mm.

Dr. Hurst decided to resort to blood transfusion, in the hope that the patient's condition would improve sufficiently to allow operation.

On February 26 transfusion was performed by Mr. G. T. Mullaby, 250 c.c. were given, the boy's father being the donor (both group ii). Improvement in the general condition was immediate and striking, much greater than would be assumed from a reference to the blood counts made at this period and given in the table below.

At the time of admission slight hoarseness was noticed; on February 28 it became much more marked, and a laryngoscopic examination showed that the left vocal cord was fixed in a position midway between abduction and adduction; the right cord moving normally.

A week later he developed a pericardial effusion; the spleen became a little larger and the abdomen somewhat distended. His condition was now desperate, and by March 16 the abdomen was greatly distended with fluid, and the bases of both lungs contained fluid. The pericardial effusion had somewhat subsided.

A blood count showed—

Hæmoglobin, 26 per cent.  
Red Cells, 2,525,000 per c.mm.  
White Cells, 1,400 per c.mm.

He had not vomited any blood for a month past, and a fæcal specimen contained no occult blood.

Dr. Hurst decided that the best course to adopt would be to remove the spleen and at the same time give another blood transfusion.

On March 18 Mr. L. Bromley removed the spleen. At the operation several pints of clear fluid escaped from the abdominal cavity, and the liver was seen to be definitely cirrhotic. There were a few commencing adhesions on the upper border of the spleen. The spleen was about six times the normal size, firm and much engorged.

For the following report on the microscopical appearances of the spleen I am greatly indebted to Dr. A. G. Gibson, of Oxford, to whom it was sent for investigation.

"The spleen presents the usual features of a chronic irritation of an inflammatory type. There is much increase of fibrous tissue, especially in the neighbourhood of the veins, which are grossly thickened, and around these also there are hæmorrhages. The process appears not to have gone on long enough for those infiltrations of iron pigment (from old hæmorrhage), in which streptothrichal threads are most typical when such are present. There is a suspicion of thrombo-phlebitis, and in one vein there can be seen a bundle of threads round a mass of leucocytes, etc., which are suspicious, but cannot be identified as an extraneous tissue."

During the operation a further 250 c.c. of blood was transfused by Dr. J. A. Ryle from the same donor as before.

On the day following the operation a blood count showed—

Hæmoglobin, 49 per cent.

Red Cells, 3,200,000 per c.mm.

For the next few days a good deal of leaking of ascitic fluid occurred through the lower end of the abdominal wound, but this gradually ceased, and thereafter no more fluid was formed.

Fourteen days later the right arm and the right side of the neck and chest became œdematous and tender, but the swelling subsided spontaneously in about forty-eight hours. It was thought that this might be due to a compensatory enlargement of lymph glands exerting pressure upon adjacent vessels. A skiagram showed an area of dullness in the posterior mediastinum which was suggestive of enlarged mediastinal glands.

Throughout the whole course of the illness there was an irregular pyrexia, until about three weeks after operation, when it gradually subsided.

From this time onwards the patient made an uneventful recovery, and was discharged quite fit on June 16, 1920, exactly four months after admission.

Since discharge from hospital the patient has remained perfectly well, and when last seen, in November 1920, he looked quite fit, not at all anæmic. No enlarged lymph glands could be felt anywhere; the liver was not palpable, and there was no ascites.

A blood count showed—

Hæmoglobin, 80 per cent.  
Red Cells, 4,190,000 per c.mm.  
White Cells, 7,400 per c.mm.

The Wassermann reaction was negative. He was still a little hoarse.

The following table shows the relation of the blood counts on various dates, to the course and treatment of the case—

	Hb. %	R.C.	W.C.	P.	L.	
1920						
Feb. 16	55	3,660,000	6200			Hæmatemesis—one pint (morphia, calcium chloride and lavage).
" 18						Hæmatemesis—one pint.
" 19						Two slight hæmorrhages.
" 22	22	2,280,000	4200			Inj. Ferri Cacodylatis mxxv o.m. et o.n.
" 26						Transfused—250 c.c.
" 27	25	1,300,000	3000			
March 8	26	1,560,000	2000			
" 16	26	2,525,000	1400			
" 18						Splenectomy.
" 19	49	3,200,000				
" 20	46	3,000,000				
" 21	45	3,050,000				
" 27	50	3,500,000				
" 30						Stitches removed.
June 16						Discharged.
Nov. 3	80	4,190,000	7400	58.2	41	

Hb. = Hæmoglobin %.

R.C. = Red Cells.

W.C. = White Cells.

P = Polymorphonuclear Cells.

L = Lymphocytes.

For the records of this case I am indebted to Mr. M. Coburn, who was Clinical Assistant in charge of the patient at the time.

The chief points of interest in this case are—

- (i) The comparatively sudden onset in view of the chronic type of lesion found in the spleen, which suggests an acute exacerbation in a chronic process, which had previously given rise to no symptoms.
- (ii) The purpura and subperiosteal hæmatoma, which are uncommon features in splenic anæmia.
- (iii) The acute development of ascites, and the absence of any recurrence after the removal of the spleen, in spite of the cirrhotic condition of the liver.
- (iv) The striking benefit produced by timely blood transfusions, without which it is safe to say that the patient would not have survived operation.
- (v) The associated paralysis of the vocal cord.

SUMMARY OF TWENTY-SIX CASES OF SPLENIC ANÆMIA TREATED IN GUY'S HOSPITAL  
SINCE 1899

TABLE A

*Cases with no Autopsy, not submitted to Operation*

Ref. No.	Name.	Age.	Date of Admission.	Chief Symptoms.	Hæm-temesis.	Blood.			Spleen.	Liver.	Ascites.	Course.
						Hb. %.	Red Cells per c. mm.	White Cells per c. mm.				
I.	Wm. T.	12	24.7.99	Epistaxis since measles and diphtheria when 2½; liability to severe hæmorrhages from slight injuries. Abdomen prominent since 2.	None.	28	3,000,000	10,700	3½" below costal margin.	4½" below costal margin.	None.	Persistent, irregular pyrexia whilst in hospital. Discharged 14.8.99. No further history.
II.	Stephen S.	39	31.8.01	Epistaxis at times. Occasional dyspepsia. Abdominal pain 8 months after getting a chill. Vomiting blood.	Many attacks.	62	2,400,000	Normal.	2" below umbilicus. Felt hard.	Just palpable.	None.	No further hæmorrhage. Discharged, condition unchanged. No further history.
III.	Harriet H.	43	20.12.1900	3 years previously noticed lump in abdomen. Menorrhagia. Repeated loss of small quantities of blood for many years.	None.	50	3,600,000	7500	Almost to ant. sup. spine.	Not enlarged.	None.	X-ray treatment. Spleen became small. Alive and well 20 years later. See detailed report.
IV.	Annie S.	37	4.10.01	3 years previously attacks of indigestion and swelling of abdomen. Had been bitten by mosquito—but no definite symptoms of malaria. Frequent epistaxis. Abdomen said to have decreased in size after a course of quinine.	None.	60	4,800,000	2500	Level of ant. sup. spine. Hard.	4" below costal margin.	None.	Irregular pyrexia whilst in hospital. No change in condition. No parasites in blood. Discharged 11.10.01. No further history.
V.	John H.	19	16.6.02	Epistaxis for previous 3 years. Lassitude. Occasional slight hæm-temesis.	Slight occasional hæm-temesis.	60	5,400,000	2800	1" above ant. sup. spine.	Just palpable.	None.	Irregular pyrexia whilst in hospital. Laparotomy - perisplenitis. Severe epistaxis during operation. Spleen not removed owing to adhesions. Recovered. Discharged 16.7.02. No further history.



TABLE A—(continued)

Ref. No.	Name.	Age.	Date of Admission.	Chief Symptoms.	Hematemata.	Blood.			Spleen.	Liver.	Ascites.	Course.
						Hb. %.	Red Cells per c.mm.	White Cells per c.mm.				
VI.	Elizabeth L.	47	1.1.05	Lump in abdomen, first noticed 3 months previously. Slight abdominal pain. Frequent epistaxis. Very septic teeth.	None.	—	3,540,000	4400	5" below umbilicus.	Not enlarged.	None.	Irregular pyrexia. Teeth removed. Discharged 9.2.05. 16 years later quite well. Spleen not palpable. <i>Vide</i> detailed report.
VII.	Annie P.	7	29.4.08	A week previously sudden attack of abdominal pain and vomited a pint of blood. Frequent attacks of epistaxis.	One attack.	58	2,900,000	3200	3" below umbilicus.	Not enlarged.	None.	Readmitted 3 times during next 9 years, each time for abdominal pain. No further hematemesis. Frequent epistaxis. <i>Vide</i> detailed report.
VIII.	Millie P.	5½	22.9.13	Full-time baby. A week previous to admission became very pale. Diarrhoea.	None.	35	2,700,000. Nucleated reds = 2800 per c.mm.	23,000	1" below costal margin. Very hard.	Just palpable.	None.	Improved. Discharged 27.9.13. Re-admitted Jan. 1914 for broncho - pneumonia. Recovered. No further history. She is a sister of Case XVII.
IX.	George C.	6½	2.6.13	Anemia. Tonsillitis. Increasing size of abdomen. Lassitude.	None.	70	2,980,000	6000	To level of ant. sup. spine. Rub audible over spleen.	Level of umbilicus.	None.	Tonsils removed. Complete recovery. 8 years later quite well. Spleen not palpable. <i>Vide</i> detailed report.
X.	Elizabeth J.	44	24.4.14	Loss of appetite for a year. Vomited blood.	Repeated attacks.	60	2,800,000	3800	Enlarged.	Enlarged.	None.	Discharged condition unchanged. Spontaneous recovery. 7 years later, no return of symptoms, quite healthy. <i>Vide</i> detailed report.

TABLE B  
*Cases with Autopsy, not submitted to Operation*

Ref. No.	Name.	Age.	Date of Admission.	Chief Symptoms.	Hæmaturia.	Blood.			Course.	Post Mortem.		
						Hb. %.	Red Cells per c.mm.	White Cells per c.mm.		Spleen.	Liver.	Other organs.
XI.	George W.	28	31.9.1900	8 months illness with shivering fits and vomiting.	None.	20	850,000	"no leucocytes."	Jaundice, diarrhoea, increasing weakness and death, 4.10.1900.	1334 grams. No microscopic report.	2200 grams. Recent peritonitis. No cirrhosis.	6 separating sloughs in cæcum.
XII.	John H.	56	8.8.03	6 years abdominal pain chiefly when standing up. Pleurisy 5 times. Heavy drinker (whisky). Liver and spleen greatly enlarged and ascites.	None.	61	5,800,000	4062	Ascites increased. No jaundice. Epistaxis, heart failure, increasing weakness and died 5.12.03.	2286 grams. Not very hard. Much increase of fibrous tissue. Malpighian corpuscles atrophied. Marked endothelial proliferation.	2630 grams. Perihepatitis. Moderate degree of portal cirrhosis.	General chronic adhesive peritonitis. 3 pints fluid in abdominal cavity.
XIII.	Ada G.	25	22.7.04	3 years anæmia, weakness and large spleen. Occasional pain in abdomen when walking.	None.	32	2,430,000	4050	Irregular pyrexia throughout. Slight ascites. Developed lobar pneumonia and died 12.8.04.	1503 grams. General hyperplasia of fibrous framework. Malpighian corpuscles chiefly normal.	2654 grams. Normal microscopically.	Enlargement of bronchial—mediastinal—and mesenteric lymph glands.
XIV.	Alfred P.	10	13.5.05	Pneumonia a month previously. After which abdomen became enlarged.	None.	—	5,400,000	2800	No pyrexia. Liver and spleen rapidly increased in size. Ascites increased. Sudden abdominal pain. Collapsed and died 26.8.05.	1150 grams. Slight excess of fibrous tissue.	750 grams. Advanced multilobular cirrhosis.	
XV.	Harriet S.	9	—7.14	Always delicate. 15 months previously nose-bleeding and swelling of abdomen.	One severe attack.	—	4,100,000	5440	Slight jaundice. Increase in size of liver, and slight ascites. Wassermann weak + given N.A.B.—slight improvement. Discharged. Later severe hæmatemesis, collapse and death, January 1915.	6 × normal in size. Very hæmorrhagic. No great excess of fibrous tissue.	Hob-nail liver, microscopically mixed portal and interstitial cirrhosis.	No obvious source of hæmatemesis found.

TABLE C  
Cases submitted to Operation

Ref. No.	Name.	Age.	Chief Symptoms.	Blood.			Date of Operation.	Spleen.	Liver.	Result.
				Hb. %.	Red Cells per c.mm.	White Cells per c.mm.				
XVI.	Joseph E.	58	Swelling of the abdomen for the previous 5 weeks. Spleen reached level of ant. sup. spine. Liver not palpable. No ascites. No hemateme- sis.	53	3,700,000	3125	28.9.07	About 15 times the normal size. No macroscopical report.	Slightly enlarged. No evidence of cirrhosis to naked eye. No macroscopical report.	5 days after operation he developed pneumonia from which he recovered. Subsequently developed erysipelae of the face and died 21.10.07. There was no leucocytosis either during the pneumonia or the erysipelae. There was an increase of 1000 cells on the pre-operative white count.
XVII.	George P.	5	Slightly jaundiced at birth. Always pale and listless. Small discrete lymph glands in neck and groins. Spleen 4" below umbilicus. Liver at level of umbilicus. No ascites. Wassermann on this occasion positive. Slight improvement with anti-luetic treatment.	20	1,900,000	21,000	26.9.12	1803 grams. 11½" in longest diameter.	Liver not cirrhotic.	Irregular pyrexia which became normal after operation. Good recovery. During next year had chicken-pox and diphtheria. Readmitted July 1914 with diarrhoea and vomiting. Left apical pneumonia and pneumo-coecal meningitis from which he died 16.7.14. A brother of Case VIII.
XVIII.	Ethel W.	10	Occasional attacks of feverishness for past 2 years, during which time abdomen slowly increased in size. Lower border of spleen 1" above pubic crest. No hematemesi- s or epistaxis.	55	5,000,000	5313	11.4.13	Marked perisplenitis. No report on condition of spleen.	884 grams. Microscopically showed numerous small giant-cell systems.	Became collapsed and died shortly after operation. P.M. Bronchial and mediastinal glands enlarged and studded with grey tubercles. Mesenteric glands caseating.
XIX.	Henry S.	12	Sudden severe attack of hæmatemesi- s lasting 36 hours. Greatly enlarged spleen and slight enlargement of liver. Wassermann reaction + No ascites. No response to anti-luetic treatment.	36	2,200,000	4050	10.3.15	Great increase in amount of fibrous tissue throughout. Many areas of hæmorrhage. Malpighian corpuscles comparatively healthy.	Seen at operation to be definitely cirrhotic.	Wassermann reaction became negative after removal of spleen. Quite well 6 years later. Sudden illness and death, Nov. 1921. <i>Vide</i> detailed report.

TABLE C—(continued)

Ref. No.	Name.	Age.	Chief Symptoms.	Blood.			Date of Operation.	Spleen.	Liver.	Result.
				Hb. %.	Red Cells per c.mm.	White Cells per c.mm.				
XX.	Thomas G.	30	An epileptic. Admitted unconscious after a fit. Had previously been unaware of enlargement of spleen which was felt 2" below the umbilicus. It had caused no symptoms. No hæmatemesis.	—	4,000,000	2100	18.5.14	No report.	1996 grams. Slightly cirrhotic.	Spleen removed with great difficulty and much loss of blood. Died 4 days later. P.M. Right sided pyopneumothorax. Enlarged oesophageal veins.
XXI.	George R.	20	12 years' history of attacks of abdominal pain. Spleen known to have been enlarged 12 years. Skin at times yellow and urine dark. Liver just palpable. Wassermann negative. General health so poor that he was unable to attend school for several years. No hæmatemesis.	65	3,730,000	9600	1.9.15	4 lb. 6 oz. Whole organ intensely congested. Large hæmorrhagic areas, many broken-down red cells and pigment granules. Moderate excess of fibrous tissue throughout. Congestion the essential feature in this spleen.	No cirrhosis found at operation.	Pneumonia immediately after operation but recovered. Has been perfectly well ever since, and served for a short time in the Army at home. Is now married and has one healthy child. When seen in April 1921, 64 years after operation, Hb. = 108%, R.C. = 4,700,000, W.C. = 12,180. Liver just palpable. Says he is perfectly well.
XXII.	Wm. McG.	16	Vomited blood at 2 years of age, and again when 8. Otherwise quite healthy. 6 years later again vomited blood and was admitted. Spleen 2" below umbilicus. Liver not palpable. No ascites. Wassermann negative.	66	4,670,000	2720	9.9.16	690 grams. Microscopically showed uniform fibrosis, and proliferation of the endothelium.	Not seen to be cirrhotic at operation.	Complete recovery. When seen in April 1921, 4 years after splenectomy, he stated that he had been perfectly well, and for the last 2 years had been working as a clerk. Hb. = 85% R.C. = 5,320,000, W.C. = 8800. Wassermann reaction negative.
XXIII.	Charles S.	51	Had a sudden attack of hæmatemesis in the night 2 years ago. Since then many such attacks. On one occasion vomited 2 pints of blood. Diagnosed duodenal ulcer at Middlesex Hospital. At laparotomy liver seen to be cirrhotic. Spleen 2" below costal margin.	52	3,500,000	1560	18.6.20	Marked increase of fibrous tissue throughout. Sclerotic nodules, corpora pignani. Slight endotheliosis of veins.	Slightly but definitely cirrhotic. Both branches of portal vein in liver were thrombosed.	Transfused during operation, but subsequently developed hypostatic pneumonia and died 24.6.20. P.M. Varicose veins found at liver end of oesophagus. Scar of old healed ulcer in duodenum.



TABLE C—(continued)

Ref. No.	Name.	Age.	Chief Symptoms.	Blood.			Date of Operation.	Spleen.	Liver.	Result.
				Hb. %.	Red Cells per c.mm.	White Cells per c.mm.				
XXIV.	Wm. McK.	22	A congenital syphilitic subject. Swelling in left hypochondrium noticed 3 months previous to admission. His general health was very bad and he was losing weight. Liver and spleen both enlarged. Rub audible over spleen. Wassermann positive.	64	4,040,000	7160	8.9.19	No report on spleen, except that there was well-marked perisplenitis corresponding with the rub heard over this organ.		He made an uneventful recovery, and is now 2 years later, in a much better state of health. A blood count was done in April 1921. Hb. = 75%, R.C. = 5,190,000, W.C. = 13,300. Wassermann strongly positive. <i>Vide</i> detailed report.
XXV.	Agnes S.	46	Frequent attacks of indigestion for the last 5 years. 2 years ago vomited $\frac{1}{2}$ pint of blood. Hematemesis again a year ago. Admitted 21.2.20.	45	2,500,000	5000	24.2.20	Microscopically showed great excess of fibrous tissue, especially around veins which were much thickened. Malpighian corpuscles atrophied. One of larger veins showed a commencing thrombo-phlebitis. Spleenic vein thrombosed.	Cirrhotic.	3 days after operation she developed pneumonia. Left-sided empyema followed for which a portion of rib was resected. Gradually became weaker and died 17.3.20. P.M. General peritonitis. Operation very difficult on account of old dense adhesions.
XXVI.	Elvin B.	14	Frequent attacks of epistaxis for some years. 3 days before admission headache and repeatedly vomited blood. Purpuric rash appeared on body. Spleen enlarged, liver not palpable. Blood transfusion given in hope that condition might be improved to allow splenectomy. Ascites occurred and increased in amount. Wassermann negative. A further transfusion given during the operation.	55	3,660,000	6200	18.3.20	General increase of fibrous tissue especially around vessels. Early thrombo-phlebitis in one vein.	Liver definitely cirrhotic.	Marked improvement after splenectomy. Ascites did not recur. Pneumonia, oedema of face, neck, and arm. Gradual recovery. Quite well a year after splenectomy. <i>Vide</i> detailed report.

## OF THE NATURE OF SUMMER DIARRHŒA

By H. C. CAMERON, M.D., Physician for Diseases of Children, Guy's Hospital.

WE are still far from understanding the causes which lead to the great increase of infant mortality and morbidity which occurs in the late summer. The total of deaths rises every year in August and September to a height which is roughly proportional to the severity and duration of the summer heat, and which corresponds amazingly closely to the curve of the records of the 4 ft. earth thermometer. Great heat in the early summer, on the other hand, causes no considerable rise in the mortality. Further, investigation shows that the deaths occur for the most part among artificially fed children, living under poor hygienic circumstances, and that the toll is greatest among the children inhabiting the ill-ventilated and crowded houses of the poorer parts of cities. A clinical study of the affected infants shows that the most usual symptoms in fatal cases are pyrexia, vomiting, diarrhœa, and a rapid dehydration of the body.

In the past it has been the usual belief that we have to deal with an epidemic of infective enteritis, due to an organism, not identified, but which is thought to be conveyed in the milk. Further, it is stated that the disease may be communicated directly from child to child and that the house-fly plays a conspicuous part in the dissemination of the causative organism. The effect of heat is regarded as acting not directly upon the child, but indirectly by encouraging bacterial decomposition of the milk. The poor buy a cheap milk, and because it is cheap it is obtained without care and is dirty. Even if a clean milk were available, in crowded and insanitary homes contamination is unavoidable.

The assumption that we have to deal with the ravages of a specific infection remains, however, without proof. The weight of evidence, indeed, appears to me to favour the contrary view, which has of recent years received increasing support,<sup>1</sup> that the prejudicial action of heat is mainly physical and exercises its harmful effect by reason of the instability of the mechanism which controls heat formation and heat loss in infancy.

It is of course admitted by all that contamination of the milk with streptococci and other pathogenic organisms derived

directly from the animal body is capable of producing epidemics of diarrhœa. In numerous instances such outbreaks have occurred and have been traced to their source, perhaps in the diseased udder of a single cow or even in a single diseased teat. No doubt too, deleterious substances derived from peculiarities or faults in the fodder supplied to the cow are capable of causing intestinal disturbance in infants receiving the milk.<sup>2</sup> The possibility of an accident of this sort undoubtedly exists. It seems certain, however, that the great rise in infant mortality in the late summer is not to be explained by the habitual and widespread presence of such accidental infection or contamination.

That the mere multiplication of the usual milk saprophytes and the presence of their products in excess in a milk otherwise uncontaminated can produce diarrhœal disorders, we have no evidence at all. The great hopes aroused when Pasteur first showed the extent to which these organisms were present in ordinary market milk, and when Soxhlett devised the simple apparatus for pasteurising milk, have been doomed to disappointment. The dangers and difficulties which surround the artificial feeding of infants are still with us. Buttermilk, teeming as it does with saprophytic milk-souring organisms, is indeed a valuable help in infant feeding, widely used in many countries with good results. Provided that the souring does not go beyond a certain point, there are no ill effects observed.<sup>3</sup> The dangerous degree of souring is accompanied by an alteration of taste so extreme that no infant will drink the milk. In milk which is very sour the content of fatty acids never reaches the height which is normal in the stomach of healthy infants during the digestion of cow's milk. In cases of severe and fulminating summer diarrhœa immediate examination of the milk taken does not show as a rule evidence of excessive souring. Nor indeed is the tendency to suffer from diarrhœa and vomiting in hot weather in any way confined to infants in receipt of cow's milk. It affects alike those who are fed upon the breast, upon cow's milk, upon dried and condensed milks, and upon the usual proprietary foods. It is difficult to understand how breast milk or even how condensed or dried milk can be so contaminated.

A clinical study of the cases of diarrhœa in hot weather does not, in my opinion, support the view that we have to do with a single disease of the nature of an infective enteritis. Rather it is clear that the mortality is made up of several types of disease, each favoured or caused by a persistently high temperature. And it is most certainly only from clinical study that conclusions of value can be drawn. Attention has been directed too exclu-

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sively to the evidence, valuable as it is, derived from analyses of statistical returns. The infant has but one function highly developed, that of absorbing food. It follows that disorders of the most various nature alike manifest themselves by disturbance of this one hypertrophied function of digestion. However the baby is ill, it is apt to show it by diarrhœa and vomiting. Deaths with diarrhœa in the summer are, in the nature of things, apt to be returned as due to "Summer Diarrhœa," or "Infective Enteritis." When the returns are analysed and plotted out into a curve, there is apparent the huge autumnal rise, which is regarded as evidence of the presence of an epidemic of infective enteritis. The curve has been co-related with another curve also dependent upon great heat and moisture, the curve of the number of flies. The deduction has been made and generally accepted that the deaths are in the main due to contamination of the milk by the agency of flies. Preventive propaganda at least appears to be based upon this argument. The importance of the need for extreme cleanliness in the milk is insisted upon. Attempts are to be made to destroy the unknown infecting agent before it reaches the child. Milk is to be boiled and cooled, napkins are to be sterilised, dust and flies are to be combated in every possible way. No one will dispute that advice inculcating cleanliness is good advice, yet it is possible that teaching insisting on the need for adopting measures to assist the young child to combat the direct influence of the heat upon its own body might be more fruitful of results. If there is good evidence that a large part of the total mortality is due to the inability of the young infant to protect itself against the ill effects of high temperature, stagnant atmosphere, and excessive moisture, our propaganda must be modified accordingly.

### THE PREJUDICIAL EFFECT OF LONG-CONTINUED HEAT UPON INFANTS

The power to maintain a normal body temperature is perhaps the most sensitive index of thriving and of health in infancy. The feeble child tends to show a temperature curve with considerable fluctuations above and below the normal. The first indication of improvement and increasing strength is shown by the recovery of the monothermia of health (Chart A). An unstable heat centre with a temperature curve showing considerable variations is constantly found in the newly born. In older infants it is a mark of weakness. After a fall in weight from nutritional disturbance of any sort, the early inconstancy of body temperature



may again show itself. Exposure to cold and an insufficient intake of food, especially of carbohydrate food, causes the sub-normal registrations to predominate. Exposure to great heat and an excessive consumption of food, especially of carbohydrate food, on the other hand, may cause pyrexia. In time of great heat the infant may well be more thirsty than usual, and since food and drink are bound up in one and the same fluid, the thirst is apt to be assuaged by the consumption of greater amounts of food. The total food required by the infant, whose surface area in comparison to its mass is relatively enormous, varies within wide limits according as the mean temperature is high or low. In time of heat the need for food and the tolerance for food falls, while the intake, because of thirst, may remain at a high level. Dyspepsia with diarrhœa and vomiting may ensue

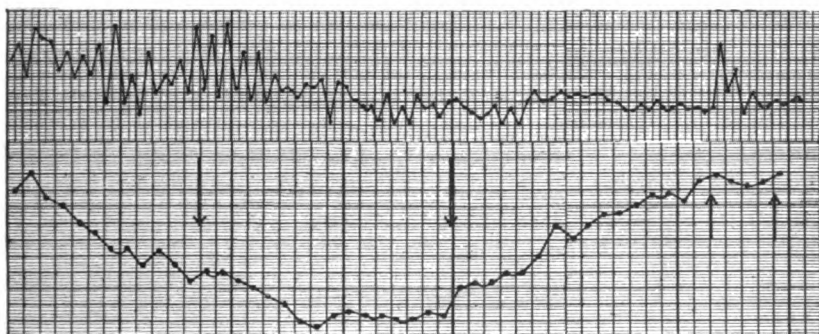


CHART A.

To show the prolonged instability of body temperature while the infant failed to thrive, and the monothermia which appears when nutrition improves.

upon an intake of food which has become excessive only because the loss of heat from the body has been greatly diminished.

Experimental work to determine the prejudicial effect of prolonged exposure to high temperatures has been attempted mainly upon young animals.<sup>4</sup> Diarrhœa and vomiting has been constantly produced. Analysis of the gastric contents under such conditions has shown a great fall in the free hydrochloric acid and in the total acidity, as well as a decline in the activity of the pepsin and rennin. It is true that attempts to investigate the same points in the case of infants confined in wards purposely superheated gave inconclusive results.<sup>5</sup> The exposure, however, was much too short to allow any deductions to be made. The danger, as the observations by Ballard upon the 4 ft. earth thermometer demonstrate, lies in the exposure to great heat over long periods. The results of bacteriological investigations upon infants dying of diarrhœa after subjection to great

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heat are highly suggestive. Except in the separate group of bacillary dysenteries, which are also rife in hot weather, the micro-organisms found in cases of severe and fatal diarrhœa do not differ from those found in healthy infants so far as examination of the stools is concerned. In the upper intestine, on the other hand, a region normally comparatively free from bacteria, an abundant growth of *B. coli* has been cultivated. An organism incapable of doing harm in the large intestine may produce substances of a highly toxic nature in another situation. It has been shown, for example,<sup>6</sup> that bacilli isolated from the intestine can convert histidin, a normal product of protein digestion, into  $\beta$ -iminazolyethylamine, a substance which has been found capable of causing diarrhœa and vomiting in infants when given by the mouth and which is absorbed only from the large intestine and not from the small. A similar overgrowth and spread of bacteria not in themselves abnormal under the influence of heat may indeed be witnessed in another and more obvious situation. The rise in the incidence of diarrhœa in hot weather is paralleled by the great increase in cases of septic infection of the skin among infants, such as pyoderma, furunculosis, etc. During the hot summer months the number of infants in an out-patient department attending with skin sepsis may increase fivefold.<sup>7</sup>

Considerations such as these support the view that the great summer mortality is not entirely or chiefly due to infective enteritis, the result of contamination of the milk supply, but is to be attributed in great part to the prejudicial effect of heat in lowering the need for food and the tolerance for food, in diminishing the force and activity of the digestive secretions, and in encouraging the overgrowth and migration of bacteria which are normal inhabitants of the colon to other parts of the bowel. Clinical observations point to the same conclusion.

### CLINICAL CONSIDERATIONS

Among infants suffering from exposure to great heat at least four groups may be distinguished.

A. A group showing some disturbance of the heat regulating mechanism, together with digestive disturbances of greater or less severity.

B. A group comprising cases of acute catarrhal, follicular, or ulcerative colitis, in which the bacillus of dysentery has been found in a varying proportion.

C. A group of cases of "heat stroke," in which cerebrospinal symptoms are the most prominent.

D. A terminal state of "intoxication."

## GROUPS A AND B

For the sake of clearness I may, perhaps, contrast the symptoms in the first two groups, A and B.

*Character of onset.*—In colitis or dysentery the onset is sudden. In the midst of perfect health the child changes colour and may be sick. Older children complain of feeling cold and may have a rigor. Within a very short time the temperature rises to a considerable height and, with much straining and tenesmus, diarrhœa, frequent and profuse, sets in. In the cases in which the heat mechanism is disturbed the onset is characteristically insidious. The appetite fails, the child seems less active, and the tissues may feel less firm. If during this prodromal period the temperature is regularly measured, the monothermia of the healthy infant will be found to have been replaced by a curve showing some irregular rise of temperature. In many cases there is continuous elevation of the temperature. Gradually digestive disturbance, perhaps of no great severity, becomes prominent.

*Age of Incidence.*—The true heat disturbance affects almost entirely infants in the first year of life. Only hypotrophic, debile children suffer in the second year. The infective colitis, on the other hand, affects young children of any age, and very usually children in the second and third year of life.

*Social Conditions.*—The true heat disturbance is confined to a very great extent to the infants in the airless rooms and scarcely less airless streets of the poorer parts of cities. Infants by the seaside, where the air even on the hottest day is in free movement, are seldom attacked. On the other hand, infective colitis occurs among the children of the well-to-do as well as in the slum, and outbreaks at the seaside or in surroundings which might be supposed ideal are quite common.

*The Character of the Gastro-intestinal Disturbances.*—In acute colitis the stool contains a great deal of mucus, and in most cases blood. There is much straining and tenesmus. Prolapse of the bowel is a not uncommon complication. Vomiting is often absent and seldom prominent. The appetite may remain good throughout.

In the true heat disturbance, after the prodromal period, appetite usually flags. Vomiting of sour material may be occasional or frequent. The stools may be loose and watery and of the usual green tint. The diarrhœa and vomiting may be severe or very slight, but it is noteworthy that from the severity of these symptoms no estimate can be formed of the degree of danger. Cases may pass into the stage of terminal intoxication

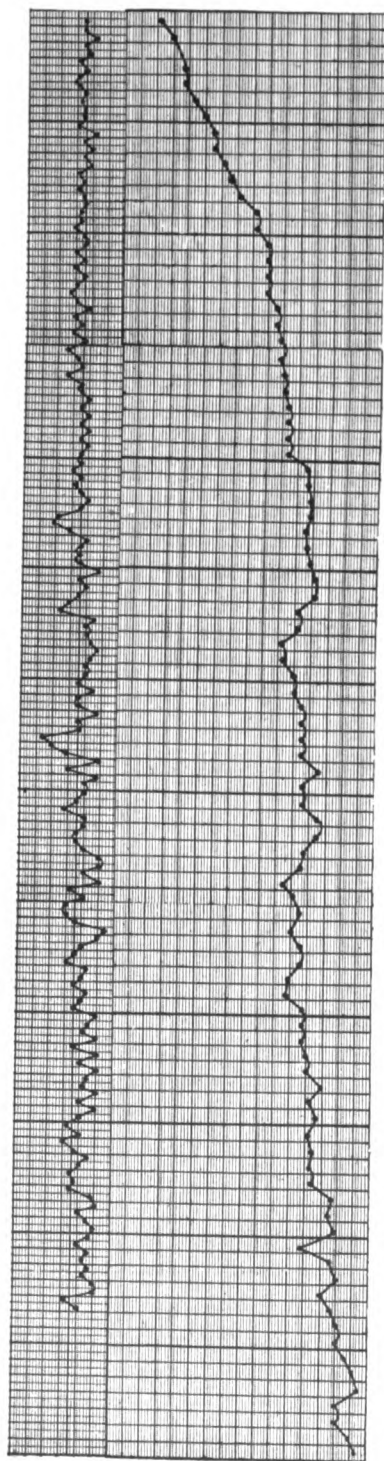


CHART B.

To show the usual correspondence between the curves of weight and temperature in acute infective enteritis. The onset is sudden and the severity of the condition at once apparent.

without any marked gastro-intestinal disturbance. In others diarrhœa and vomiting may be profuse. In colitis, on the other hand, in which the disease is primarily located in the bowel, it may be said that the severity of the diarrhœa is proportional to the degree of disturbance of the general health and the extent of the danger.

*The Relation Between the Curve of Weight and the Curve of Temperature.*—In acute follicular colitis the two curves in general vary inversely (Chart B). The temperature rises abruptly and falls gradually. The weight curve shows an initial fall, as a rule most steep in the first forty-eight hours, and only after the temperature has fallen to normal does the weight curve flatten and finally again begin to rise. In feeble wasted infants pyrexia may be absent or slight.

In the heat disturbance, on the other hand, the rise of temperature and the fall in weight bear no constant relation to each other. In not a few cases we may find a steady gain in weight while the temperature is rising ominously and the child is growing

fretful, pale, and anxious (Chart C). A terminal fall in weight of great severity is almost constant, while at the end the temperature either falls to subnormal or shows a still further rise. In the early stages another and very significant contrast may be demonstrated. Withdrawal of all food for twenty-four hours or longer will in no way influence the temperature curve of a case of colitis. Starvation in a true heat disturbance, on the other hand, in the absence of any terminal or complicating infection, may promptly bring down the temperature. Cases of heat disturbance in which no terminal intoxication has developed recover with remarkable rapidity when cool weather returns. When symptoms of intoxication, which may be due

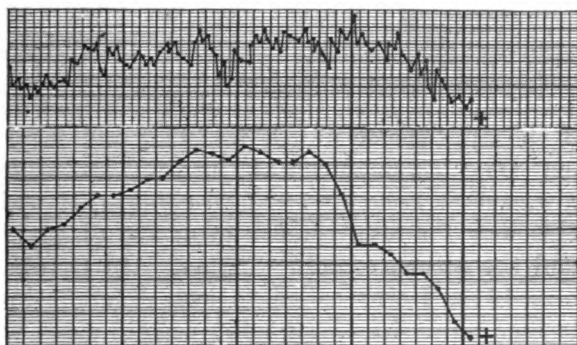


CHART C.

To show continuous pyrexia with initial increase of weight, and gradual development of intolerance for food, during a time of great heat, with terminal dehydration, intoxication, and death. Until the end of the third week the child showed no alarming symptoms.

to endogenous infection of the small intestine, have developed, disappearance of the heat wave or removal of the child to the seaside are without effect.

*Course and Prognosis.*—The course of cases of colitis is often short. The fever and diarrhœa commonly abate after four or five days. There is, however, a considerable tendency to relapse. In a few cases, almost always in young infants, a chronic and ultimately fatal ulcerative colitis is established. The course of the heat disturbance is more difficult to measure because the onset is so insidious. The pyrexia is seldom apparent to the mother. It is discovered only by the thermometer. In colitis, on the other hand, the child is often in a burning heat. The outlook in colitis in older children above one year of age is good. Epidemics of true bacillary dysentery among children in this country appear to be rare, though

doubtless many remain unidentified. In 1918 I met with a localised epidemic in a suburb of London in which the Shiga bacillus was found. Several of the cases proved fatal. Acute colitis in older children on the whole occasions little alarm. In infants the rule is that the child recovers from the colitis, the blood and mucus disappear, the temperature falls, but the nutritional disturbance may have been so great that the child is left in a condition which makes it peculiarly prone to develop the symptoms of a true heat disturbance, if it is still consistently exposed to the high temperature. This change of type is frequently encountered, and appears to have been peculiarly common in the year 1921.

The prognosis of the true heat disturbance depends upon the possibility of removing the child from the great heat. It is important that the intake of food should be promptly curtailed. Once the body temperature has risen and the child has begun to show intolerance for food, there is always present an increasing risk of the appearance of the terminal and fatal stage of intoxication. The development of the fatal intoxication may be very slow, and it is common to be confronted with infants dying in this way for many weeks after the disappearance of the heat and the return of cold weather. On October 28 and November 2, 1921, I was called to two different institutions with wards for infants to advise upon certain cases which had only then begun to show the symptoms of "intoxication." The last case at Guy's was brought to hospital with a diagnosis of meningitis upon November 4.

#### GROUP C

In a small number of cases the effect of heat is sudden as in heat stroke. To judge by the literature, cases of this sort appear to be more common in America and on the Continent, where the temperature in the shade reaches greater heights than with us. The child is brought to the hospital unconscious, often with convulsions or with muscular rigidity and opisthotonos. The onset has been absolutely sudden. The temperature from the first is very high, 105° to 107° F. With cold sponging or with rectal irrigation with cold water it may fall, but a large number of such cases end fatally within a few days. In this group also the diarrhœa and vomiting appear to be only incidental. The most striking symptoms are the high pyrexia and the evidence of cerebrospinal irritation. Two cases of heat stroke of this nature were admitted to the children's ward from the surgery during September 1921.

## GROUP D

As a terminal and almost uniformly fatal stage we meet with the condition known as "intoxication." The whole aspect of the child is altered. The face grows anxious and haggard, with expressionless eyes fixed apparently upon some point in the distance. Only when the child cries does the vacant look disappear. The skin is pale and grey. The subcutaneous tissues have lost all their firmness and tension, and the whole body of the child is dehydrated. The eyes are sunken and the fontanelle depressed. The breathing is deepened and amplified—the so-called "air hunger" or "hunted breathing." The movements of the limbs are slow and feeble. The arms are apt to be held stiffly flexed, or kept in constant slow movement in front of the chest—the "boxer position." Glycosuria, albuminuria, acetonuria are often found, and serve to indicate how complete is the breakdown of the metabolic processes of the whole body. After death in most cases the liver is found to be fatty. The bowel shows no evidence of enterocolitis. In this terminal stage the diarrhœa may be even less prominent than before.

This very striking condition develops in the majority of all cases of heat disturbance which have a fatal ending. In its absence, indeed, recovery under suitable treatment may be confidently expected. When once it has supervened we know that the end is likely to be fatal. No treatment has proved effective. Like uræmic or diabetic coma, it is a terminal stage, in which treatment in general comes too late.

We are still ignorant of the explanation of these symptoms. According to one widely accepted view the acid products of excessive intestinal fermentation, which have in the first place produced the heightened peristalsis, ultimately, under suitable conditions, so interfere with the activity of the epithelial lining of the intestine that absorption of toxic substances derived from protein disintegration is permitted. Against these the liver, for a time at least, acts as a second line of defence.<sup>8</sup> Others regard all the symptoms as dependent directly upon the anhydræmia and renal insufficiency.<sup>9</sup> To me it seems likely that the symptoms of intoxication accompany the endogenous infection of the small intestine referred to above, an infection to which exposure to great heat predisposes by diminishing the anti-septic force of the digestive juices and by producing dehydration of the body.

## PRACTICAL CONCLUSIONS

It is a matter of great moment that we should determine the relative importance of the two factors which may be principally concerned in the production of summer diarrhœa. Is heat in the main prejudicial because it encourages contamination of the milk supply with pathogenic bacteria, or is it prejudicial because of its physical effect upon the child, the infective element being both endogenous and terminal, occurring only after the resistance has been profoundly lowered and after great dehydration of the body? If the disease is due to contamination of the milk supply, then we may rest content to lay emphasis upon the need for cleanliness in the handling of the milk, upon the need for destruction of flies and the disinfection of the dejecta of children already infected. If the effect of heat is physical, the stress must be laid upon measures to assist the child to withstand its attack.

We may recommend—

(1) That in hot weather food should be reduced as a routine measure by a considerable percentage, while the total volume of fluid is kept the same or increased. Especially the intake of carbohydrates should be lowered.

(2) That attention should be paid to securing that the clothing by day and night should be light and porous. A single garment may be sufficient at times during the heat of the day.

(3) That tepid or cold sponging should be practised as a routine.

(4) That the hangings of cots and cradles should be done away with for the time being, permitting the circulation of air as freely as possible.

(5) That the child should occupy a room with a through draught, in which the air can if possible be felt in free movement.

The ideal room for a young child is one which has windows opening upon opposite walls of the house, so that a current of air proportional in strength to the difference in temperature between the wall in the sunshine and the wall in the shade runs through the room. Since this is seldom available, a room should be chosen of which the door opens into a space ventilated from the opposite wall of the house. From the impossibility of securing this, many modern blocks of flats in which the windows all point one way and the doors open upon an ill-ventilated corridor, are as unsuitable for young infants as are the old and discredited back-to-back houses.

(6) That care should be taken not to add to the moisture in



the air of the room by cooking or washing of clothes, or bathing in hot and steaming water.

(7) That the number of persons in the room should never be increased unnecessarily.

The infant enveloped in many layers of impervious flannelette, lying on a feather bed in the most airless corner of an airless room, which is crowded with adults, and opens only upon a courtyard in which the temperature is 90° in the shade, an infant whose restlessness and crying and thirst are soothed by the free administration of an artificial diet, is under conditions peculiarly well fitted to produce the disturbance of body temperature which leads to a loss of tolerance for food, to bacterial overgrowth within the intestine, to endogenous infection and ultimately to intoxication. To urge the mother of such an infant to practise rigid cleanliness in the handling of the milk, or to demand a low bacterial count of milk saprophytes per cubic millimetre in the milk, are measures not in themselves sufficient.

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## TWO CASES OF ADOLESCENT KNOCK-KNEE

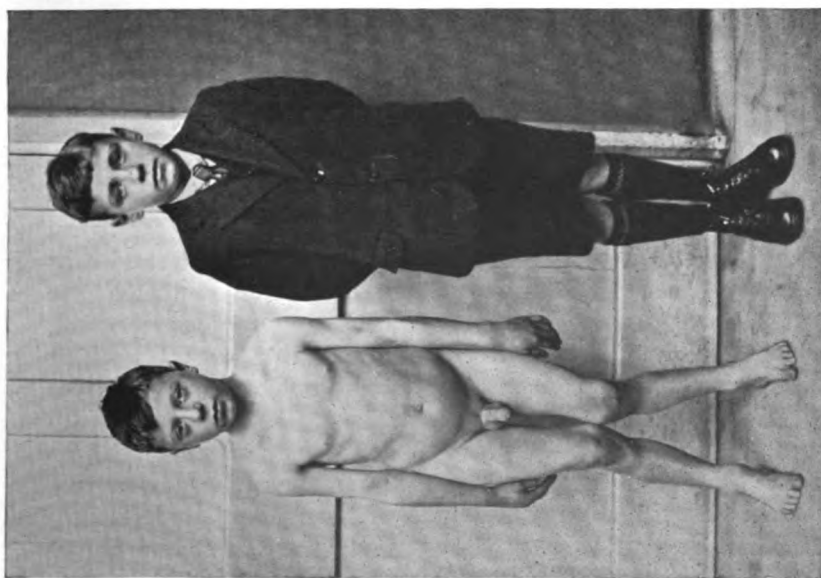
### I. A TYPICAL RENAL DWARF

### II. LATE RICKETS WITHOUT OBVIOUS CAUSE

By HUGH BARBER, M.D., Physician to the Derbyshire Royal Infirmary.

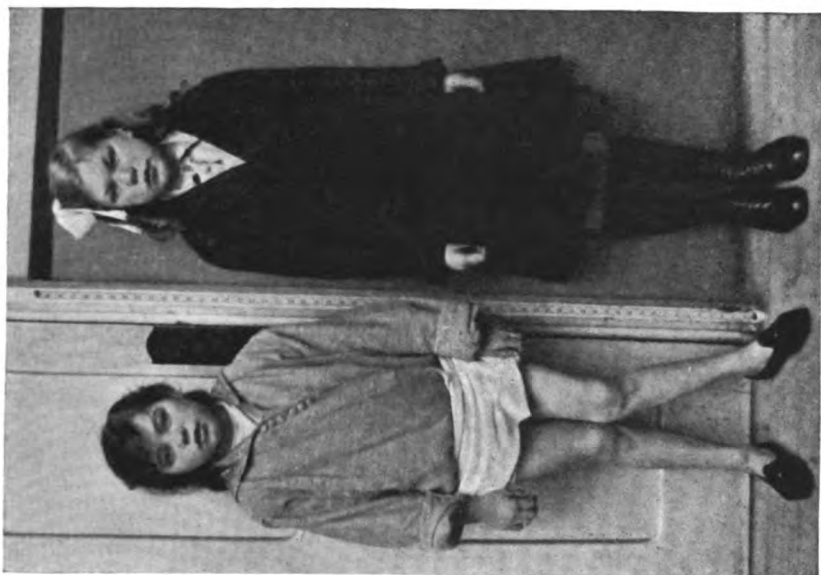
THERE are certain clinical types in medicine of which the nomenclature is never very satisfactory. Cases which may be grouped under the heading of "late rickets" are an illustration; for it is a clinical picture which is indicated rather than an ætiological or a pathological entity. Since 1911, when Morley Fletcher, Miller, and Parsons called attention to the association of bone deformities of late rickets type with interstitial nephritis, evidence has been accumulating steadily that this is a disease not very rare. Sometimes called renal infantilism, more usually now renal dwarfism, it is recognised at clinical medical meetings, if not yet in text books. Renal dwarfism is the more suitable designation, as was first pointed out in some notes from this hospital, in which an extreme degree of the stunted development had not prevented the occurrence of menstrual periods.

Interstitial nephritis in children has been recognised for a long time; one has seen cases without late rickets symptoms; but the bone deformity picture, which develops usually towards puberty, and is frequently the condition for which advice is sought, has, I think, only been described since 1911, with the striking exception, which I have not seen quoted before, of a paper by Clement Lucas in the *Lancet* of June 1883, entitled "A form of Late Rickets associated with Albuminuria." He records that he has seen this association too frequently for it to be a matter of chance. But he regards the albuminuria as functional, and does not discuss the quantity of urine or the specific gravity, which might have indicated a more serious kidney lesion. Moreover the cases were not observed for very long, and he gives a favourable prognosis, which is in marked contrast to the cases seen here, which eventually have a fatal termination. But I do not remember hearing any reference to Mr. Lucas' observation, not even from himself, during my years at Guy's; and I am interested to think that I am recalling,



CASE I.

Renal Dwarf aged 13½ yrs. Brother aged 8 yrs.



CASE II.

Late Rickets aged 14 yrs. Sister aged 11 yrs.

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in the Reports of his hospital, his work on the subject after nearly forty years.

Case I in this paper is the twelfth case of renal dwarfism of which I have made notes since 1911. Case II is a late rickets case without obvious visceral lesion to produce the bone deformities; and although neither the numbers nor the records are sufficient to justify any dogmatic statement of the relative frequency of the interstitial nephritis cases, I think it is fairly accurate to say that in this hospital, of cases presenting themselves as adolescent knock-knee, about two out of three will be renal ones. The interstitial nephritis is easily overlooked, because the cardio-vascular changes are singularly slight; and albuminuria, although present constantly in most cases, is occasionally absent on one or two isolated occasions, and, more difficult still, has not been detected at all in one or two recorded cases proved post-mortem.

### CASE I. A TYPICAL RENAL DWARF

W. C., male, aged  $13\frac{1}{2}$  years, was brought to hospital in June 1921, on account of recently developed genu valgum. He had attended in 1917 for a month or two for enuresis.

His father and mother are healthy. There are nine children living, of which the patient is the eighth; the brother, aged eight years, shown in the photograph, is the youngest. All the others are quite healthy, but there were three more who died; one from diphtheria, one a few days after birth, and one after premature birth at eight months. There have been no miscarriages. During pregnancy in this case the mother was quite well, but much distressed about her child with diphtheria, who died at this time. He was a full-term child, and was brought up on Nestlé's milk, but suffered from sickness. He was rather below the average at birth, but, although small, developed fairly well till six or seven years of age; after which he seems scarcely to have grown. He did not walk till just over two years old, but his legs were straight. He has had no illnesses. When about six years old it was noticeable that he drank a lot of cold water, and passed an unusually large quantity of urine. At times he complained of headache. In February 1917, when aged nine years, he attended the Derbyshire Royal Infirmary for nocturnal incontinence: he was much undersized, but there were no evidences of rickets, and the legs were straight. He took thyroid for a month or two, and was then lost sight of. The urine was not examined.

In June 1921 he returned on account of knock-knee, which had developed comparatively quickly about two months previously. He was now much undersized: height 3 feet 8½ inches (12 inches below the normal); there is no pubic or other hair on the body, but the external genitals are fairly well developed for his size. His face is healthy. He has a moderate degree of thirst, but is otherwise well. The epiphyses are much enlarged; the knees, ankles, and wrists most obviously so, and there is "beading" of the ribs. X-ray photographs show very irregular ossification. The heart is normal, the arteries scarcely, if at all, thickened, the blood pressure 100 m.m. The urine has specific gravity 1006 to 1014; albumen is present (<1 pt. per 1000); the quantity is about 3 pints per diem. The Wassermann reaction is negative.

The thirst, polyuria, with low specific gravity, and albuminuria, associated with the characters depicted in the photograph, are absolutely characteristic.

The following are the chief features which this patient shows in common with other renal dwarfs observed in Derby—

(1) Absence of any evidence of a cause of the nephritis, or any evidence that the lesion commenced as a parenchymatous condition.

(2) Insidious onset, as indicated by the diagnosis being overlooked in 1917.

(3) The development of genu valgum comparatively suddenly about puberty (there has been one exception, in which it developed earlier).

(4) The slight constitutional symptoms, apart from late rickets.

(5) The slight cardio-vascular changes.

From experience of the other cases, one may conclude—

(6) That the case will probably terminate fatally some time in the next five or six years; and

(7) That marked interstitial nephritis will be found post-mortem.

## CASE II. LATE RICKETS WITHOUT OBVIOUS CAUSE

This case is described by way of contrast, and may be regarded as one of late rickets.

M. P., female, aged fourteen, was brought to hospital on account of recently developed genu valgum.

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Her father and mother are healthy; there are seven other healthy and well-developed children.

She was fed on the breast for twelve months, as the other children were. Her teeth were cut at usual age, and she walked at eleven months. She was in every way normal until ten years of age, when development appeared to cease. She has had no infectious disease, but is stated to have had pleurisy when aged six years. She appears quite well in health, but the legs became crooked when she was about thirteen.

Her height is 4 feet 6 inches ( $3\frac{1}{2}$  inches below average); genu valgum is present, but there is not much evidence of rickets in other epiphyses. Pubic hair is present and development of breasts is commencing, but there has not yet been any menstrual period. The urine is normal, with specific gravity 1020, and average amount per diem 30 to 40 oz. The spleen is hard and palpable  $1\frac{1}{2}$  inches below the costal margin; the liver edge is just palpable and feels normal; there is no jaundice. The blood is normal; red corpuscles and hæmoglobin are not diminished. There is no leucocytosis. The Wassermann reaction is negative. The x-rays show much less than in a renal dwarf case.

This case is one out of five or six that have been carefully investigated to exclude kidney disease since renal dwarfism has been generally recognised here; and if these cases of adolescent knock-knee are to be regarded as late rickets, there would seem to be very little evidence that there has been recrudescence of a former infantile rachitic condition. The bony changes, as shown by the x-rays, are not so marked as in the renal dwarfs.

More complete investigations from the chemical pathology point of view may give more definite data to explain the ætiology of both renal and other cases.

These notes can only claim to illustrate the condition, and to demonstrate that in this hospital about one case per year of renal dwarfism presents itself, most probably seeking advice for genu valgum. The contrast to Clement Lucas' notes of forty years ago is that, if the cases are followed up, they are found to end with uræmia, most usually between fourteen and sixteen years of age, but with very little clinical warning. Surgical interference is therefore unwise, because it may precipitate, or, perhaps more likely, seem to precipitate such a termination. A support for the legs has enabled several of the patients to get about quite well for a year or two.

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## **“VICIOUS CIRCLE” OR REGURGITANT VOMIT- ING AFTER GASTRO-JEJUNOSTOMY**

By R. P. ROWLANDS, M.S., Surgeon to Guy's Hospital.

THE results of gastro-jejunostomy in suitable cases of non-malignant disease are, on the whole, very good. Failures are chiefly due to jejunal ulceration and to vicious circle. Much has been said of the former<sup>1</sup> and curiously little of the latter. This gives a false impression of the relative frequency and importance of these two complications, which may also be associated with each other. Vicious circle, always serious, is often a grave complication, spoiling the result of the operation or even leading to death if adequate measures for its correction are not taken in time.

The object of this communication is to discuss its causation, prevention, and treatment. The following remarks are based chiefly on personal experience of a considerable number of cases seen and treated during the last fifteen years.

### **ÆTIOLOGY**

Regurgitant vomiting is due to variable degrees of intestinal obstruction at or near the anastomosis, where the jejunum becomes kinked, compressed, or rotated. It is usually the result of faulty technique, due to want of care or lack of experience, but in some cases it is caused by adhesions, contractions, or displacements developing some time after the operation. It is often due to the opening in the stomach being made in front, too high, or too far to the left, or to the opening in the jejunum being too low, so that a loop is left between the duodeno-jejunal flexure and the anastomosis. This loop gets water-logged and heavy or displaced, causing kinking at the stoma. The danger of a loop is almost avoided by making the stoma close to the origin of the jejunum, but in some cases the opening has been placed too near the duodeno-jejunal flexure, so that the latter, being immovable, has become kinked by the drag of a dilated stomach in the process of contraction. In other cases the segment of jejunum proximal to the anastomosis has passed



through the small gap left between the transverse meso-colon, the root of the mesentery, the spine and the anastomosis, and has thus become obstructed.

Frequently the jejunum at the stoma has been drawn up into or through the meso-colon by the retraction of a dilated stomach rapidly diminishing in size; the opening in a thick or short meso-colon has contracted round the bowel, bringing the proximal and distal jejunum parallel, and causing an acute kink or spur between them.

#### MECHANISM OF VICIOUS CIRCLE

The obstruction may affect one or both limbs of the jejunum, but usually the afferent limb alone at first. This limb gets over-distended with bile, pancreatic juice, and food, and then compresses the parallel efferent limb, or displaces the spur between the two limbs, causing a more or less complete, but high, intestinal obstruction. This is the essential mechanism of vicious circle.

The contents of the distended duodenum usually enter the stomach at the stoma but sometimes they regurgitate through the pylorus. Vomiting ensues and brings temporary relief. In a quiet period food may pass freely from the stomach into the distal limb of the jejunum, as shown by radiography, and the diagnosis may thus be missed.

The passing of a considerable amount of bile and pancreatic juice into the stomach after gastro-jejunostomy is a normal event, as is proved by withdrawing and examining the gastric contents. The good results of the operation largely depend upon the neutralising action of these alkaline secretions within the stomach. In normal individuals this does not induce vomiting, which is only caused by stasis due to obstruction at or near the stoma.

The discharge of all the bile into the stomach does not necessarily cause vomiting, as shown by the absence of this symptom after cholecystogastrostomy for irremovable obstruction of the common bile duct. Steudel's<sup>2</sup> experiments completely prove that the escape of all the bile and pancreatic juice into the stomach did not cause vomiting in dogs, and that the same is true in man is shown by Moynihan's case of complete traumatic rupture of the duodeno-jejunal flexure, where the end of the duodenum was closed and the jejunum was joined to the stomach and the patient did not suffer from vomiting.

## SYMPTOMS AND SIGNS

There are two chief clinical types, distinguished as acute and chronic vicious circle.

In the former, the obstruction being more or less complete from the time of the operation, the vomiting comes on in a few days; it is violent and generally fatal unless it is promptly relieved, whereas in the latter type, the obstruction being incomplete or intermittent, the symptoms are less severe, the vomiting occurring only about once or twice every two or three days or weeks.

The vomiting is characteristic. Bilious fluid regurgitates in large quantities at various intervals, usually without much effort or pain. The vomit has a peculiar, offensive smell, but is never enteric or fæcal, although it may be very dark from altered blood. The acute attack is sometimes accompanied by severe epigastric pain with intolerable thirst and rapid wasting.

Slight degrees of obstruction do not cause vomiting, except in nervous individuals, but nausea, pain, and anorexia are not uncommon and are usually temporary, though they may be more or less permanent.

## DIAGNOSIS

Regurgitant vomiting has to be distinguished—

(1) from that due to the anæsthetic, which is now rare, transient, and comparatively trivial;

(2) from that due to hæmorrhage, which ceases with the bleeding;

(3) from that due to paralytic distension of the stomach, which is promptly stopped by lavage;

(4) from that due to intestinal obstruction lower down, which can be detected by the brown, enteric character of the vomit; and

(5) from that due to peritonitis—a very rare complication—by the absence of rigidity of the abdomen.

An x-ray examination carried out during an attack generally affords valuable information as to the exact state of affairs which are giving rise to the vomiting (Fig. 1).

## PROPHYLAXIS

The prevention of regurgitant vomiting depends almost entirely upon careful attention to every detail of the operation. The latter should not be performed in the absence of visible

and palpable ulceration or stenosis of the stomach or duodenum. The stoma must be at the lowest part of the posterior surface of the stomach and as close as possible to the beginning of the jejunum, and should be large enough, but not too large. A very large opening tends to draw up and kink the jejunum. The latter must not be kinked or rotated, and too much of its wall should not be engaged and drawn into the anastomosis, or a spur will be liable to develop. For the same reason the opening in the meso-colon should be closed by sutures engaging the stomach and not the jejunum or anastomotic line. This is especially important when the meso-colon is unusually thick

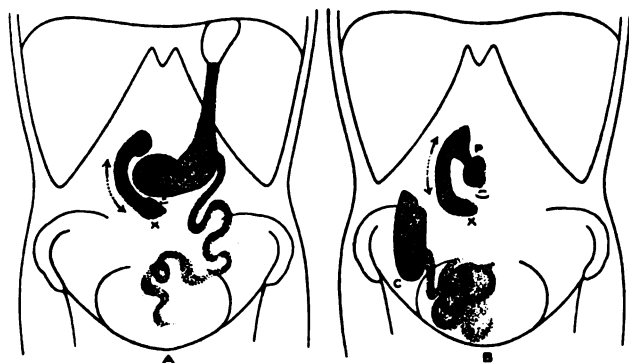


FIG. 1.

Vicious circle and gastro-jejunal ulcer with severe pain, biliary vomiting, and hæmatemesis after gastro-enterostomy performed three years before for duodenal ulcer. A shows rapid passage into jejunum through stoma, and dilated duodenum, contents of which were seen to pass violently backwards and forwards owing to vigorous peristalsis of duodenum attempting to overcome obstruction at X. B, drawn seven hours later, shows bismuth-containing chyme still present in dilated duodenum, from which it passes back through incompetent pylorus P, owing to violence of peristalsis. Findings confirmed at operation, at which the operation shown in Fig. 4 was performed (A. F. Hurst).

or short; sometimes it is better to perform Finney's operation under these circumstances, or, failing this, anterior gastro-jejunosomy. Gastro-duodenostomy is to be preferred for very nervous patients, especially women, but unfortunately it is not always practicable owing to dense and extensive adhesions and ulceration.

It is significant that a vicious circle becomes less and less common in the practice of surgeons of large experience in gastric surgery. Clearly the risk of the complication decreases with the improvement of technique and the formation of a more ideal anastomosis in the anatomical, physiological, and surgical sense. Such makeshifts as entero-anastomosis or Roux's "en-Y" method are unnecessary and are to be avoided whenever

possible, because they are more liable to be followed by jejunal ulceration.

After the operation it is important to raise the shoulders, and to avoid overloading the stomach by the early administration of too much food and especially drink.

### TREATMENT

(a) *Lavage*.—For acute regurgitant vomiting gastric lavage, repeated if necessary once or twice a day, is often successful, but, if the vomiting is severe and continues in spite of this, an early operation becomes necessary to save life. For chronic or subacute cases lavage should be tried for a longer period and is occasionally successful.

(b) *Operations*.—1. *Entero-anastomosis* is the operation

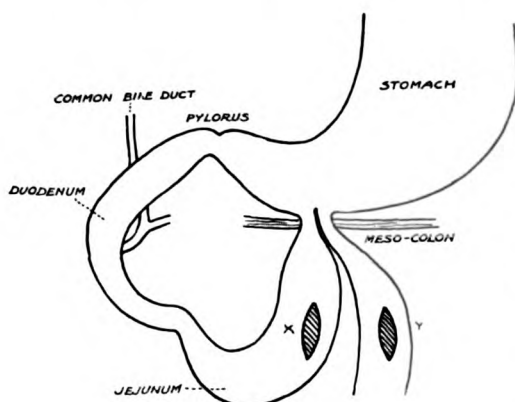


FIG. 2.

Lateral entero-anastomosis for relief of a vicious circle after gastro-enterostomy. The openings made at X and Y are joined together.

generally advised, the bowel proximal and distal to the gastro-jejunostomy being joined together as far away from the latter as possible (Fig. 2). After the modern posterior operation this is not easy owing to the immobility of the parts far back to the left of the lumbar spine. A pillow behind the loin often helps. The terminal part of the duodenum

may need mobilising by dividing the parietal peritoneum to the left of it.

In many cases the operation is successful in saving life or alleviating the symptoms, but it sometimes fails completely and is often only partly successful, nausea, anorexia and occasional vomiting persisting or recurring.

2. *Entero-anastomosis with closure of the proximal limb of the jejunal loop* is practically always successful (Figs. 3 and 4). Failure of complete relief with the prospect of still another operation, or as an alternative chronic invalidism, is especially to be avoided in these cases, and for this reason I strongly advocate this operation in preference to simple entero-anastomosis.

3. *Abolition of the gastro-jejunosotomy* with restoration of the natural anatomy is the obvious treatment in the few cases where neither ulceration nor stenosis is found at the pylorus or in the duodenum.

I have had considerable experience of this grave complication with some of my own early cases and, in many more instances, where I have been called to see patients who were either *in extremis* from acute vicious vomiting about a week after the operation, or emaciated and miserable invalids after a long period of chronic reflux vomiting. Sometimes, after performing

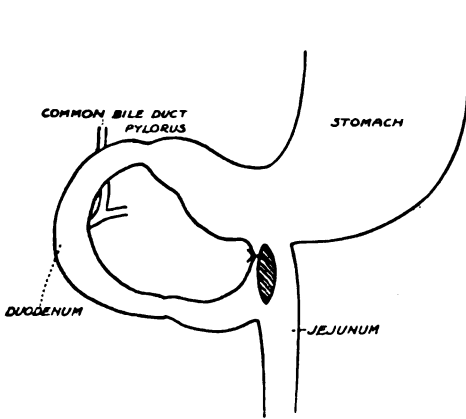


FIG. 3.

Ligation of proximal jejunum with lateral entero-anastomosis for relief of a vicious circle after gastro-enterostomy.

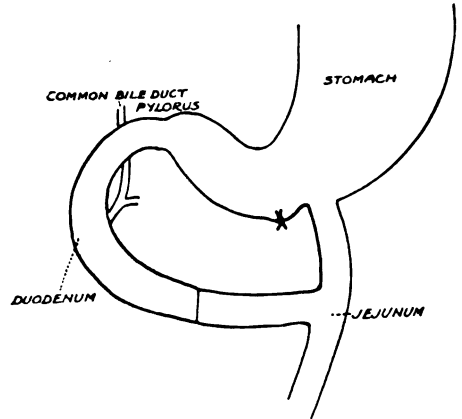


FIG. 4.

End to side anastomosis for relief of a vicious circle after gastro-enterostomy, the proximal jejunum having been divided and its gastric end closed.

entero-anastomosis in vain, I have had to re-operate to close the jejunum on the proximal side of the gastro-jejunosotomy. Few operations can be more trying than these, the exact nature of the former operation being sometimes unknown, and adhesions, displacements, and distension of the proximal jejunum adding to the difficulties.

#### DETAILS OF THE OPERATION

In acute cases it is wise to wash out the stomach before commencing, and generally to make a fresh incision to the left of the middle line and lower than the usual gastric incision in order to give a more direct and uncomplicated access to the anastomosis. A rubber pillow behind the upper part of the loin will here again be found of assistance.

The transverse colon and the great omentum are freed from adhesions and held up by an assistant, and the anastomosis

found and freed from adhesions. This is a step which is often difficult owing to distension of the jejunum and inflammation and œdema of its walls and the ascent of the stoma into or through the meso-colon. The proximal part of the jejunum must be clearly defined, and to do this it may be necessary to mobilise the fourth part of the duodenum by dividing the peritoneum near its left border. The proximal part of the bowel ascending to the stomach is either divided or else crushed and ligatured an inch below the anastomosis. The latter method is by far the easier and quicker, but it is not quite so satisfactory as division with closure of the gastric end and implantation of the rather short duodenal end into the side of the distal jejunum. If ligation be chosen, the ligature must be buried by a circular sero-muscular suture and a lateral anastomosis performed below the ligature.

Division of the proximal jejunum is especially valuable when the latter is short or stretched, thus acting as a tractor on the gastro-jejunosomy or duodeno-jejunal flexure and kinking one or both. It also helps to mobilise the parts to be engaged in the new anastomosis, which is thus made easier. It is rarely possible to deliver the parts concerned in the anastomosis; they must, therefore, be carefully emptied, clamped, and packed off to prevent contamination.

After this operation the risk of gastro-jejunal ulceration would seem considerable, but I have no knowledge of its occurrence in any of my cases, some of which date back fifteen years.

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## THE HETEROMORPHOSES IN THE HUMAN BODY

By G. W. NICHOLSON, M.D., Lecturer in Morbid Histology, Guy's Hospital.

ON account of the difficulty of thoroughly examining living tissues, normal development and growth have been studied chiefly by means of fixed material. One stage only is preserved, and conclusions as to the course development has taken and the causes by which it has been influenced can only be drawn from a comparison of many different stages. It has thus come about that an elaborate experimental technique has been evolved. The normal course of development is interfered with by the infliction of a given injury. The study and interpretation of the results form the basis of the greater part of our knowledge of the mechanism of growth and development.

Nature constantly performs experiments of the same kind, but on a very much more varied and extensive scale. Many of these are drastic indeed. One extreme is represented by double monsters, in some of which all the tissues of the body are implicated. The other comprises the small tissue malformations, in the slightest of which one kind of tissue is alone affected.

Some of these tissue malformations are so slight that they do not even deserve the name of malformation. For they consist of perfectly normal cells, joined to their surroundings in an orderly manner. These anomalies of position, which are usually spoken of as "heteroplasias" by pathologists, and as "heteromorphoses" by biologists, are perhaps the most interesting of them all, since they are simple enough to convey hints of the causes that have produced them.

Monsters and their near relations, the complex teratomata, seem to suggest that the body is a mosaic and that, even in the most adverse conditions, a cell ultimately surmounts all obstacles and differentiates into its predestined shape, unless indeed it perish in the attempt. The simple heteroplasias and allied conditions, on the other hand, indicate most clearly that a certain amount of latitude is allowed to the forms that cells can assume. Because of the evidence they afford of a "regula-

tion " of growth they are of great value, since they corroborate the results of experiment.

This contradiction of each other by the extremes of the series is, I feel sure, only an apparent one. The causes that have produced a monster must have acted at so early a stage of embryonic life that we can form no idea of the conditions then obtaining; the interpretation of their results is therefore well-nigh impossible. On the other hand the slightest of the tissue malformations have taken place but yesterday; in the later stages of embryonic life or even in the adult body. Hence reliable deductions can sometimes be drawn from them.

I have therefore collected instances I have observed of the slightest of the tissue malformations, together with the most important references to them from the literature.

#### I. AN EPITHELIAL HETEROMORPHOSIS IN PROCESS OF FORMATION

The heteromorphoses, when we see them, are usually Nature's finished experiments. The tumour that forms the first part of this paper is an unusual instance of an unfinished experiment. It is an "embryonic tumour" of the kidney of an infant, a class of neoplasm whose distinguishing feature is the close and unmistakable, although distorted, manner in which it recapitulates the normal development of that organ.

These tumours are made up of a blastema of round cells, which gives rise to their other components. It differentiates in two opposite directions, forming on the one hand the connective tissue and on the other the epithelium of the tumour. Tubules originate as rosettes of round cells surrounding small areas of granular ground substance. Lumina appear in these, and the cells enlarge, acquire definite bodies and outlines, and become epithelial in type. The resulting tubules often undergo a considerable degree of differentiation into structures closely resembling, and comparable with, the secreting tubules of the kidney.\*

The specimen under consideration differs from the majority of the embryonic renal tumours in the presence of glomerular formations, which display the phenomenon I wish to draw attention to. Since they never contain capillaries, but are otherwise comparable with stages of development of glomeruli, I shall refer to them as pro-glomeruli.

\* For accounts of these tumours see Hedren, *Ziegler's Beitrage*, 1907, xl. 1; also Trappe, *Frankfurter Zeitschrift f. Pathologie*, 1907, i. 130. The latter emphasises their close relationship to malformations and shows that they are malignant embryonic kidney "anlagen," whose only real difference from the kidneys of the embryo is that they do not differentiate fully.



*Description of Specimen* (Figs. 1-6).—The blood-vessels are thin-walled and distended with blood. There are no true capillaries in the tumour, their place being taken by small cracks and spaces between the connective tissue fibrillæ. They are quite indistinguishable from ordinary tissue spaces except for the presence of an occasional red blood corpuscle, which adapts its outlines to those of the space it occupies. These corpuscles are easily visible in sections stained with eosin (*vide* Fig. 3, in which two are depicted in a triangular space near the top of the drawing, and a single elongated one in the crack to the right of the tubule near its lower end).

The pro-glomeruli are formed in the following manner: Tubules are met with, the epithelium of one part of which consists of a single layer of fusiform or flat cells, which merge

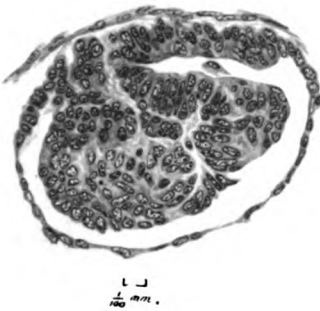


FIG. 1.

Embryonic tumour of kidney. Solid epithelial pro-glomerulus, surrounded by flat cells of Bowman's capsule.

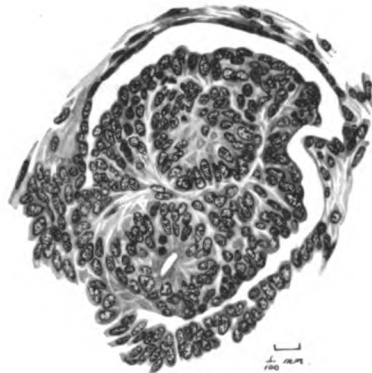


FIG. 2.

Aggregation of epithelium of pro-glomerulus to form solid masses, in the lower of which a lumen has appeared.

rather suddenly with the columnar epithelium lining the rest of their circumference. The latter becomes folded or invaginated into the lumen and twisted upon itself, to form solid epithelial structures (Fig. 1), which differ from developing glomeruli in the absence of capillary blood-vessels. The part of the circumference of the original tubule that is lined by flat epithelium forms a structure analogous to Bowman's capsule.

The pro-glomerulus increases in size. The oval and round nuclei at its periphery show little tendency to become flattened (Fig. 4); usually they retain their original shapes. Those in its body group themselves into more or less isolated clumps, near whose centres they tend to become pyknotic and to disappear (Fig. 2, upper half). Lumina appear in the centres of the clumps (Fig. 2, lower half), the cells surrounding them become columnar and stratified (Figs. 3-5), mitoses are found

in them near the lumen (Fig. 5), which becomes sharply defined. The tubules grow and become twisted. They form secondary attachments to the cells of Bowman's capsule (Fig. 5), and tend to grow out into, and to fuse with the tubules of, the general parenchyma of the tumour. Large masses of tubules, still lined by remnants of Bowman's capsule, result from their growth (Fig. 6). Eventually they become indistinguishable from the general parenchyma.

I have not been able to satisfy myself that pro-glomeruli are ever formed a second time. The early stages described

above were all found in comparatively undifferentiated parts of the parenchyma of the tumour, one of which is represented in the upper left-hand corner of Fig. 6. I have seen no appearances suggestive of this possibility.

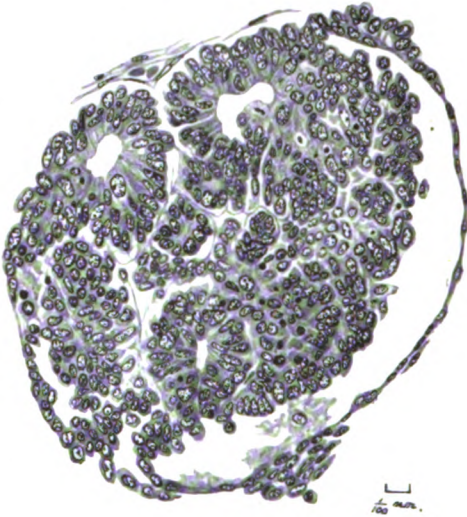


FIG. 3.

Growth of pro-glomerulus, and formation of tubules within it. The lower one of these probably formed by invagination of surface epithelium.

Normal differentiation of these pro-glomeruli invariably stops at the stage illustrated in Fig. 1. Except for the complete absence of capillaries, the pro-glomerulus closely resembles a glomerulus of the developing kidney.

Differentiation at this point always becomes abnormal. With very

few exceptions (Fig. 4) the nuclei of the pro-glomerulus, instead of assuming a flat shape, are locally condensed into spherical masses, at the centres of which they degenerate and disappear. Rosettes, typical of the first stage of tubule formation in embryonic tumours of the kidney, are thus produced (Figs. 2-5). The nuclei at their periphery elongate and take up a radial position. Cytoplasm accumulates on their central aspect and cylindrical cells result. A lumen appears at the centre of the rosette, and a tubule is formed in exactly the same manner as are those that arise directly from the blastema of the tumour. Proliferation of the nuclei of the pro-glomerulus constantly takes place. It appears to be amitotic, since karyokineses are absent at this stage. New rosettes are formed and these again acquire lumina (Fig. 3).

In other words, the epithelium of a pro-glomerulus, such as that drawn in Fig. 1, contains the potentiality to differentiate in two directions. One of these is the normal one, characterised by flattening of its cells; it is followed only in a few exceptional instances (Fig. 4). In the vast majority of cases differentiation proceeds in a direction contrary to the natural one; all the characters of tubular epithelium are assumed.

The question arises, Why should this marked deviation from



FIG. 4.

Increase in size of tubules of pro-glomerulus.

normal development occur, and why does it always take place at the same moment, just when the epithelium of the pro-glomerulus ought to assume its permanent flattened form?

There are two possible answers to this question. Either, the cells are abnormal and cannot differentiate further in a natural manner. The cause here lies in the cells themselves. Or, they are normal and able to do so, but do not succeed from causes external to themselves.

I can see no reason, on purely theoretical grounds, to assume a *vitium primæ formationis* until all other explanations of an

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anomaly have failed. Such an assumption is, after all, merely a way of closing the discussion. Again, tumours obey the laws that regulate the growth and development of the other tissues of the body in a most surprisingly accurate manner, as I have attempted to show elsewhere.\* A phenomenon, merely because it occurs in a tumour, is never to be regarded as a thing without a parallel in normal development.

The earlier stages of the development of the pro-glomeruli have been quite orderly, and Fig. 4 shows that the epithelium on their surface does sometimes assume a flat shape. It must



FIG. 5.

Secondary attachments of tubules to Bowman's capsule. A mitosis in the largest tubule near its lumen.

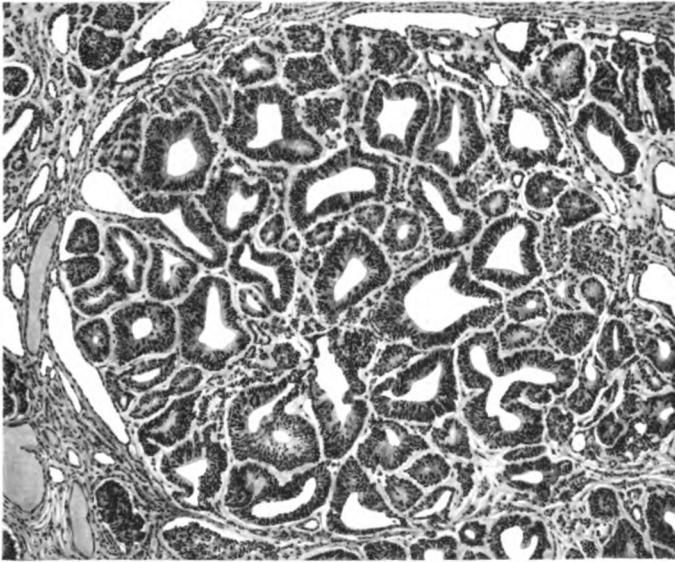
therefore be admitted that its cells possess the potentiality to differentiate fully. I therefore see no reason which renders the assumption indispensable that the cells are not inherently normal.

That the permanent flattened form of the glomerular epithelium is the expression of its complete differentiation is undeniable. At birth, and for a considerable time afterwards, many glomeruli are lined by cubical cells. Herxheimer<sup>17, 18</sup> has published some suggestive observations on the kidneys of infants in their first year of life. In about 88 per cent. of those he examined he was able to demonstrate the presence of a quite considerable number of small glomeruli with collapsed and therefore inconspicuous capillaries. They

\* *Guy's Hospital Reports*, 1921, lxxi. 222.



were lined by cubical epithelium with deeply stained nuclei, and conveyed the impression of great cellularity. He regards them as arrests of development. His observations justify the conclusion that the definitive flattening of the glomerular epithelium is the result of functional stimulation. Its office is, I take it, to allow the passage of fluid from the capillaries into Bowman's capsule. The flatter the cells are, the less resistance do they offer to it.\*



1/10 mm.

FIG. 6.

Growth of tubules of pro-glomerulus to form nodule nearly 1 mm. in diameter. Tubules have fused with those of general parenchyma, but remnants of Bowman's capsule remain.

The deduction is therefore justified that, if the capillaries are absent, the stimulus which induces the cells to assume the flat form is absent as well. They therefore do not, and indeed cannot, assume this shape. Since they are unable to differentiate in the direction that depends on their stimulation by the presence of glomerular capillaries, they do so *in the*

\* That flatness of an epithelium is a sign of functional activity, and that its maintenance demands a certain effort, so to speak, is corroborated by the alveolar epithelium of the lungs. In pathological conditions, in which the pleura is thickened and the superficial alveoli rendered inactive, it is an everyday occurrence to find them lined by large cubical cells with round nuclei. I am sure that no one who examines sections of a fibroid lung of long standing for the first time will guess that the branched tubules he sees, lined by cubical and columnar cells, which look more like secreting glands than anything else, are nothing more than the remnants of the pulmonary alveoli.

*only other possible direction.* They form tubules after the manner of all the epithelial cells of the developing kidney that do not come into this intimate contact with capillaries. Herein they follow the line of least resistance. I would particularly emphasise the fact that the line of differentiation assumed is the only possible alternative one, since it appears to me to be the keynote to the understanding of the manner in which the heteromorphoses are produced.

As long as cells are at a stage of development at which their prospective potentialities have not, as yet, been completely unfolded this result is bound to happen when they are affected by abnormal stimuli. For the absence of a natural stimulus is clearly capable of producing an abnormal result, and is therefore to be regarded as a form of abnormal stimulation. If the conditions outside the cells at a critical moment of their development, at which they ought to proceed to differentiate in one direction, are such that they are unable to do so, they will inevitably do so in the other possible direction; provided, of course, that the conditions are not sufficiently abnormal to inhibit further development. The disturbances that can give rise to big results can be very slight indeed; for the earlier they act during development, the greater are the prospective potentialities of the cells at the time. The greater and more varied, therefore, will be the resultant malformations.

It follows that the heteromorphosis can consist only of tissues that are within the prospective potentialities of the cells at the moment of its formation. We shall see the importance of this when we come to examine some of the finished heteroplasias that are met with in the body. It follows too that they can no longer arise once the cells of a part have acquired their permanent tissue characters.

The abnormal stimulus, be it a defective tissue correlation, as in the present instance, or be it some other abnormality, may leave no other trace of its action behind it. Nor is it to be expected that the resultant malformation, when finished, should furnish us with evidence of the cause of its origin. Who, on looking at the big mass of tubules in Fig. 6, would guess that it has arisen from the epithelium of a pro-glomerulus into which no capillaries had penetrated?

The present observation bears a close resemblance to the famous experiments of Herbst.<sup>14, 15</sup> In place of an extirpated eye, he was able to produce, in certain crabs, either the same organ, or the distal part of an antennula. The nature of the product of regeneration depended solely on whether he removed or preserved the optic ganglia, which are not regener-

ated in these animals. If they were preserved, visual impulses were transmitted by the regenerating nerves, and the cutaneous cells differentiated into perfect eyes. If the ganglia were removed, these impulses could no longer be transmitted. The regenerating nerves took on the only possible alternative function and transmitted tactile impulses to the brain. The cells of the epidermis with which they were connected produced tactile hairs, and an antennula, or organ which carries these hairs, was regenerated. These experiments demonstrate the relation of cause and effect in as clear a manner as our own observation; in the latter the disturbance is, however, much finer.

Herbst's experiments bring out very clearly the importance of the interdependence of the tissues of the body, the one to the other, in the final effect that is produced. That the development of a normal individual must depend on the orderly correlation of its parts is, of course, an obvious fact. No two cells of the body can be placed in an identical position in regard to their surroundings. It is these slight differences that produce the variations in the cells that are known as differentiation. It is inconceivable that an ovum should develop into an individual consisting of so many parts, were all the cells, as they divide, subjected to identical stimulation. But it is not often that a defect of the orderly correlation of parts can be demonstrated in respect to cause and effect as clearly as in the case under consideration.

*Conclusions.*—There are two possible explanations of the mechanism by which development and differentiation take place: preformation and epigenesis. Our observation seems to indicate that the course of evolution undergone by the cells during their development depends only in part, and that a minor one, on their pedigree. Quite as important, if not more so, are the stimuli that affect them. Position in the body, in relation to the surface and to other cells, appears to be the chief of these. When the stimuli are normal, but only so long as they are, the cells of a given part will inevitably assume their stereotyped forms. If they be abnormal, or if the normal stimuli be absent, an abnormality of structure will as inevitably result. Every stage of development is the result of, the expression of, the stages that have gone before. When there is an abnormality, it has a cause external to itself. We need not invoke the aid of a *vitium primæ formationis*.

I cannot resist, as a pathologist, drawing attention to the possible bearing the specimen under discussion has on the causes of tumour formation. The bulk of the nodule in Fig. 6

is about a thousand times greater than that of the pro-glomerulus in Fig. 1, assuming them both to be roughly spherical in shape. And this is not the end, since mitoses, too small to be indicated in Fig. 6, are very numerous in the epithelium of the tubules. In how far may not the unlimited growth of a malignant tumour depend therefore on some defective correlation of its parts, because of which differentiation of its cells cannot take place? Since full differentiation is incompatible with rapid proliferation, must not its cells continue to divide for ever? It is outside the scope of this paper to enter into these questions. The inception of the tumour is not explained by the defective correlation, it merely suggests a possible cause for its unlimited "malignant" growth.

## II. THE HETEROPLASIAS

A brief review of the principal heteroplasias that are met with in the body must now be given. For reasons that will become apparent later on, I include under this heading only those conditions in which there are no signs whatever of inflammation, past or present.

*Upper Cardiac Glands of Œsophagus* (Fig. 7).—The most fully developed and frequent, as well as the best known of them all is found in the upper part of the œsophagus, at the level of the cricoid cartilage. Schaffer<sup>41</sup> was the first to demonstrate that, in about 70 per cent. of all bodies, patches of gastric mucous membrane are to be found here. The glands that constitute them always correspond to those of the cardia. These heteroplasias are therefore commonly spoken of as the "upper cardiac glands" of the œsophagus, to distinguish them from the lower cardiac glands, which are scattered in an irregular manner in this organ, close to its opening into the stomach.

These glands are usually bilateral, a patch of them being found on either side of the middle line. They vary enormously in size. The smallest, according to Schaffer, consist of only one gland, that opens on to the surface between two of the papillæ of the œsophageal mucous membrane. The largest I have seen measured fully a centimetre in their longest diameter. Their surface is pink and velvety, and slightly below that of the surrounding squamous epithelium. They can easily be mistaken for shallow ulcers. Under the microscope the surface is seen to consist of a covering of tall columnar cells, distended with mucigen. It dips downwards to form the ducts of glands, whose openings give the surface its velvety appearance. These glands are of the type of the cardiac and of the fundal glands, the latter of which possess chief and oxyntic cells.\* The fundal

\* The ragged and irregular appearance of the glands in Fig. 7 is due to post-mortem digestion. I was unable to avoid this appearance, as I did not wish to render the drawing too diagrammatic.



glands are absent in a considerable proportion of cases. I find that the periphery of the patches, where they abut on the squamous epithelium of the œsophagus, always consists entirely of cardiac glands. The transition from œsophageal to gastric epithelium is absolutely sharp; islands of the former may occur on the surface of every part of the latter, the glands usually extend for a short distance beneath them. The heteroplasia is always entirely superficial to the muscularis mucosæ, which limits it externally. It is thus easily distinguished from the mucous glands of the œsophagus. Its stroma is delicate and scanty, and consists of a few fibroblasts, capillary blood-vessels and leucocytes. Lymphoid follicles are frequently met with, especially near the edges.

This heteroplasia consists of groups of cardiac and fundal glands of the stomach, with chief and oxyntic cells, held together by a scanty stroma, resembling that of the gastric mucous membrane. It lies entirely within the mucous membrane of the œsophagus, and is bounded externally by its muscularis mucosæ. It is everywhere sharply defined from the epithelium of this organ. When sufficiently extensive, it is covered by epithelium identical with that lining the surface of the cardia.

The regularity and typical appearance of the cells, and the orderly manner in which they are joined to the surrounding œsophageal mucous membrane, are characteristic. There are no signs whatever of malformation. The only abnormality that can be perceived is one of position. These heterotopic glands are nothing else than tiny areas of cardia let into the upper part of the œsophagus; they are stomachs *en miniature*.

Thanks mainly to Schridde<sup>44</sup> we know something of their

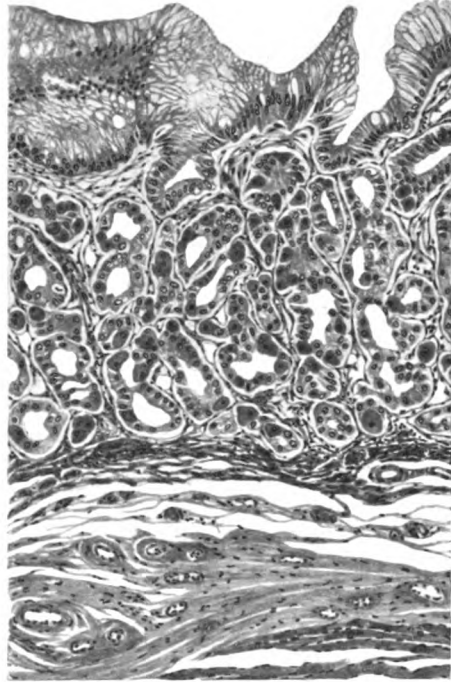


FIG. 7.

Upper cardiac glands of œsophagus, with chief and oxyntic cells. Bounded below by muscularis mucosæ.

inception. In his monograph on the development of the mucous membrane of the human œsophagus, he shows that the permanent squamous epithelium does not make its appearance until the seventeenth week (length of foetus = 100–105 mm.). At this stage the basal layer of cells that lines it shows the first signs of fibrillation. In an embryo of 105–110 mm. he found a group of five tall cylindrical goblet cells among the squamous basal cells in a recess at the side of the œsophagus at the level of the cricoid cartilage. They represent the first “anlage” of the upper cardiac glands.

As Schridde's observations are of importance for a correct appreciation of the changes that occur in the metaplasias of epithelium, it becomes necessary to summarise them. In the youngest embryos examined the œsophagus is lined by a single row of clear, cubical endodermal epithelium. By about the fifth week (length 13 mm.) it has differentiated into two layers of clear cylindrical cells. During the tenth week (length 44 mm.) ciliated cells appear. Shortly after this, in the twelfth week (length 62 mm.) the lining consists of three or four rows of clear, cubical cells, resembling those of a transitional epithelium. During the seventeenth week the cells of the basal layer become fibrillated in the manner of squamous epithelium. They divide and give rise to the permanent epithelium of the œsophagus. He insists strongly that it is only the cells of the basal layer that divide and give rise, step by step, to all these different kinds of epithelium. The tall cylindrical clear cells, the ciliated cells and the clear cubical cells are in turn desquamated and lost. Vestiges of the two latter may, however, persist until birth.

We can therefore locate the time of formation of these upper cardiac glands with accuracy. It corresponds to that of the first formation of the permanent epithelium of the œsophagus. It appears that the cells of this organ, at this stage of their development, possess the prospective potentialities of giving rise to squamous and to cylindrical epithelium.

That the whole of the œsophageal epithelium, at this stage of its development, contains the prospective potentialities of both kinds of cell, is shown by the occurrence of the lower cardiac glands near its opening into the stomach. This fact is brought out even better by the occasional presence of cylindrical epithelium in other parts of the organ. Thus Schridde found an isolated goblet cell at another level in the embryo of which an account has been given. Ribbert<sup>39</sup> found columnar goblet cells at the apex of a traction diverticulum of the œsophagus at the level of the bifurcation of the trachea.

These changes possess the one factor in common that they

are all found within recesses, where the conditions do not call for the presence of tough squamous epithelium. This has been sufficiently emphasised by Schridde. It appears probable that one of the factors that determine the character of the œsophageal epithelium is the pressure and friction that its opposed surfaces exert on each other in the fœtus. This is the stimulus in response to which the epithelium becomes squamous. In sheltered recesses it is absent, and differentiation, therefore, takes the only possible alternative course. Mucous secreting columnar epithelium results, which, at this particular level, undergoes differentiation into gastric glands.

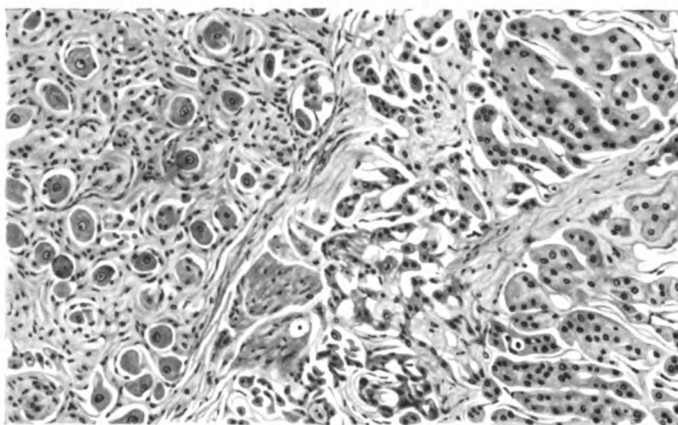
The fact that glands of the cardia only are found in this heteroplasia, and never those of the pylorus, indicates that the alternative, or recessive, prospective potentiality of the permanent cells of the œsophagus in the fœtus is the dominant one of those of the part of the intestinal canal that is situated next to it.

*Other Heteroplasias of Alimentary Tract.*—Full accounts of these are to be found in the writings of Schridde<sup>45</sup> and of Herxheimer.<sup>18</sup> I have nothing to add to them. Poindecker<sup>87</sup> describes a polypus of the small intestine covered by gastric mucous membrane. Islands of squamous epithelium in the stomach have been recorded on several occasions (see Herxheimer). Foges<sup>10</sup> has recently described a case in which the mucous membrane of the rectum, for a distance of 8 cm. above the sphincter ani, was lined by strips and patches of sharply defined, strongly keratinised squamous epithelium with papillæ and a definite corium. The condition was, apparently, congenital. Herxheimer<sup>18</sup> (p. 243) has observed islands of typical squamous epithelium in an otherwise healthy duct of the pancreas. I cannot do more than mention here that the epithelium of the gastro-intestinal tract, to the level of the omphalo-mesenteric duct at any rate, appears to possess the power to form pancreatic tissue in the embryo (Albrecht<sup>1</sup>).\*

*Heteroplasia of Medulla of Adrenal* (Fig. 8).—The following case can, I believe, be best explained as a heteroplasia. I give, with reserve, a brief abstract of the post-mortem report, which does not appear to be very accurate. The patient, a woman of thirty-eight, had suffered for some time from typical symptoms of Addison's disease, with marked pigmentation. The only abnormality found at the autopsy was a subacute atrophy of the liver with marked evidence of regeneration of hepatic tissue. The suprarenals are said to have been normal.

\* I have seen an accessory pancreas on the cardiac portion of the stomach.

I only possess microscopic slides of one of these. They have not been chromated, and I cannot, therefore, make very definite statements about the medulla. The cortex presents no abnormalities, except for the presence of a few hyperplastic nodules. Within the pigment layer there are some narrow strips of cells which correspond in appearance to those of the medulla. The greater part of this layer is, however, absent, its place being occupied by numerous small nodules of sympathetic ganglion cells embedded in nerve fibres. Nerve bundles issue from these. I believe that, owing perhaps to an abnormal correlation of the cœlomic and the sympathetic parts of the



$\frac{1}{10}$  mm.

FIG. 8.

Heteroplasia of medulla of suprarenal, with production of ganglion cells.  
Two nerve bundles between it and deep aspect of cortex.

organ, differentiation of the cells of the latter into chromaffine tissue did not take place. Their development proceeded in the only other possible direction, and ganglion cells resulted. The date of this heteroplasia corresponds to the time at which the indifferent primary sympathetic cells become differentiated into sympathoblasts and phæochromoblasts.

*Heteroplasias of Female Organs of Generation.*—Islands of squamous epithelium have been found in the uteri of children. The largest of these has been recorded by v. Friedländer.<sup>11</sup> Meyer<sup>31</sup> found cervical epithelium in the vagina of a monster with double uterus and vagina. Schridde<sup>44</sup> figures cervical glands on the vaginal surface of an imperforate hymen.

This appears to me to be the best place to mention my own<sup>36</sup> record of the occurrence of sebaceous glands in the

stump of a cervix uteri five years after hysterectomy. I attributed their presence to a prosoplasia of the islands of squamous epithelium found under the cervical mucous membrane by Meyer.<sup>31</sup> I drew attention to a record of Brünings,<sup>6</sup> who demonstrated a microscopic slide of a polypus of the uterus which contained a hair, with cortex and medulla, a cuticle, and an inner and outer root sheath. Veith<sup>51</sup> has described sebaceous glands in the anterior and posterior walls of the vagina, 1½ cm. above its external orifice, in a virgin of fifty-five. Whether prosoplasia or heteroplasia be their true explanation, the formation of these epidermal structures from mesoblast is a very remarkable fact.\*

*Conclusions.*—The anatomical features that have been described warrant the following conclusions concerning the prospective potentialities of the epithelial cells of the embryo at the time at which their permanent characters are acquired: †

(1) In the parts of the body examined, and probably in all the others as well, the epithelia possess the potentiality to undergo development in two directions. One of these may be spoken of as dominant for the part, the other as recessive.

(2) The recessive character may replace the other in every part of an organ or segment of an organ, and a heteroplasia results. The frequency with which it does so varies within wide limits at different levels.

(3) Both characters at first appear in their simplest form, the alternatives, in hollow viscera, being squamous and columnar epithelium.

(4) Heteroplasias, when they consist of columnar epithelium, may undergo a lowly form of differentiation, goblet cells being produced. On the other hand, their differentiation may attain the maximum of complexity.

(5) In the latter case heteroplasias show us that the recessive character of an organ or segment corresponds to the one that is dominant in the organ or segment next to it.‡

(6) The epithelium of the small intestine, at least down to the level of the omphalo-mesenteric duct, possesses the potentiality to form pancreatic tissue. This power is shared by that of the stomach.

\* These observations are too few to allow of deductions. My object is simply to record them, in the hope of inducing others to do the same.

† The embryological evidence, slight though it is, indicates that heteroplasias always occur at this period of development and never subsequently.

‡ *E. g.* upper cardiac glands of œsophagus, fundal glands in small intestine, cervical glands in vagina, ganglion cells in medulla of adrenal. Herxheimer's<sup>18</sup> record of squamous epithelium in a pancreatic duct indicates that the upper part of the small intestine and its glandular outgrowths share with the stomach the power to produce œsophageal epithelium.

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On summarising these conclusions and on comparing them with those we have drawn in the first section of this paper, it becomes obvious that they afford valuable indications of the processes by which development and differentiation proceed. They show that the ability to produce a certain tissue need not be strictly limited to the one spot at which it is found, but is often inherent in comparatively wide areas of the body. The wide distribution of pancreatic tissue alone is sufficient to demonstrate this. Albrecht<sup>1</sup> has pointed out that, in seeking for the explanation of the appearance of the earliest "anlage" of the pancreas, we are forced to look beyond the conditions that are found in the duodenum alone. The ability to produce this tissue is shared by a large part of the intestinal canal. Therefore some stimulus outside the epithelial cells themselves must liberate it. As a rule this stimulus acts on one area only. In exceptional circumstances it, or one very similar to it, does so at another spot as well. The cells react to it in the typical manner, and a second independent pancreas, one that we call an accessory organ, is here produced. In other words, the potentialities inherent in the tissues require outside influences to unfold them.

Heteroplasias are of importance from another point of view. They teach us to form a just estimate of structures that are often spoken of as atavistic, and as reversions to an ancestral type. Friends, to whom I have shown the upper cardiac glands, have often asked me if I know of a lower vertebrate in which analogous structures are the rule. I do not know of one, and have never taken the trouble to find out, because these and allied anomalies indicate nothing more than that the explanation of their presence is to be found in the ontogenetic history of the individual who carries them. We have seen that heteroplasias are differentiations in a direction which is usually recessive. Other anomalies are hypoplasias in the first instance, followed by differentiation into simple structures. Branchial cysts are good illustrations of this. Cases occur in which a part of a branchial pouch does not differentiate into thymus, etc., but remains at the stage of development of the primitive pharynx. But differentiation, in these cases, is not quite in abeyance. It proceeds on a lower plane, that of the lining epithelia. A cyst results, that is lined by a mucous membrane of squamous epithelium, of ciliated respiratory epithelium, or of both. Its presence does not necessarily imply that its owner is descended from fishes, but only that something has gone wrong during his development. It would be every bit as reasonable to infer that symelican monsters are

reversions to the Phocidæ. There is yet another group of anomalies that must be mentioned here. It is exemplified by supernumerary mammæ. They occur in man, not because the lower mammals happen to possess several pairs of breasts, but simply because the embryo possesses a mammary ridge, every part of which is liable to fail to involute according to the general rule. This anomaly is a persistence at an earlier stage of development, followed by orderly differentiation. That the embryo recapitulates the history of the race is quite a different story. Many short cuts are taken in development, and many stages of the evolutionary history are omitted entirely. I have never met with an anomaly that corresponds to one of these obsolete stages. I have used the term "anomaly." "Variation" is perhaps a better one to apply.

In conclusion, heteroplasias and the other anomalies touched upon in the preceding paragraph suggest that development and differentiation of a tissue at every stage is a parting of the ways. Two alternatives present themselves. One of them is adopted and becomes dominant, the other recessive. We shall see, when we discuss metaplasias, what evidence there is of the subsequent fate of recessive characters, whether they are cast off for ever, or only suppressed. Heteroplasias give no answer to this question.

Another line of thought suggests itself. The prospective potentialities of the cells at every stage of their development depend on their ontogenetic history. If we trace development backwards, we find that as each earlier stage is reached, more and greater potentialities are contained in the cells. Thus we reach the primitive germinal layers and eventually the ovum. In heteroplasias, all of which are produced in late stages of development, tissues are never found that are not contained within the prospective potentialities of the germinal layer to which the heteroplasia belongs; nor must we expect to find them. Thus, ganglion cells have never been seen in a heteroplasia of the alimentary canal, as one of its intrinsic constituents. In cases in which they are found in connection with hypo- and mesoblastic organs, they are always a part of a teratoma.\* Whether these malformations, for teratomata are malformations that present themselves to us as tumours, are susceptible of an explanation analogous to that of simple heteroplasias, is a question that I cannot attempt to discuss here.

\* The suprarenal, because of its developmental history, forms an exception.

## III. THE PROSOPLASIAS

The degree of differentiation which an epithelium attains, varies according to its situation.

The different forms of squamous epithelium demonstrate this.

The epidermis consists of a rete mucosum with prickle cells and intracellular fibrils. Its basal row of cells is more or less cylindrical in shape. It is succeeded by a stratum granulosum, whose cells are charged with globules of keratohyalin. Next in order comes the stratum lucidum. This is covered by the stratum corneum, whose dead cells have been converted into horny flakes, the most superficial of which are constantly desquamated. The deepest part of the epidermis forms papillæ. Sweat-glands, hair-follicles and sebaceous glands arise from it during its development. The degree of differentiation that the epidermis and its appendages attain is a high and complex one. It varies widely in different parts of the body.

The squamous epithelium that lines mucous membranes never attains the maximum degree of differentiation possible. In the œsophagus, for instance, it does not proceed beyond the production of keratohyalin on one side, and of short papillæ on the other. In the vagina keratohyalin is not normally produced. Differentiation stops with the rete mucosum, whose superficial cells are swollen and surrounded by a membrane, their nuclei persisting.

The bladder, the ureter, and the pelvis of the kidney are lined by a "transitional" epithelium, built up of about four layers of cells, the two basal ones of which are rounded or cubical, the middle pear-shaped, and the superficial roughly triangular, since they fit between the rounded ends of the pear-shaped cells. The structure is identical in the endodermal and the mesodermal parts of these organs. Schridde<sup>44</sup> has shown that this transitional epithelium is a true squamous epithelium, since its cells possess fibrillæ, which pass from cell to cell in the form of prickles. Differentiation has, in this instance, merely stopped at a low level.

The degree of differentiation an epithelium attains at a given spot is known as its "normoplasia." In pathological conditions, and especially in chronic inflammations and suppurations, it is exceeded. This differentiation beyond the degree that is typical for the part is spoken of as "prosoplasia."

Thus, in chronic inflammations, the cells of the mucous membranes of the œsophagus and vagina keratinise freely. Carcinomata of these organs often contain much horn.

Much more remarkable and far more interesting are prosoplasias of the urinary passages. Fig. 9 represents a part of the



pelvis of a tuberculous kidney. It is covered by an epithelium consisting of a row of more or less elongated basal cells, a thick layer of typical prickle cells, a well-developed stratum granulosum with coarse granules of keratohyalin and a thick horny layer which is desquamating, the superficial parts of which have not been drawn. Near the deep aspect of the rete mucosum a small intra-epithelial connective tissue papilla can be seen. I may add that, when suitable stains are employed, beautiful fibrils are revealed within the prickle cells. The transitional epithelium has, in this case, vindicated its claim to recognition as a squamous epithelium.

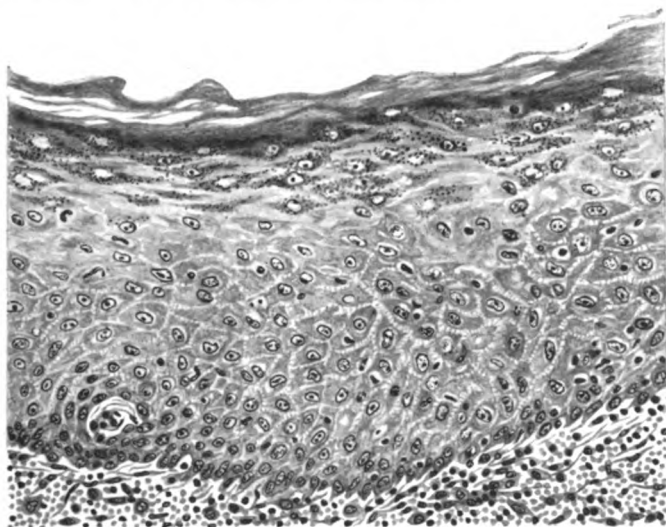


FIG. 9.

Prosoplasia of epithelium of renal pelvis.

Prosoplasias of glandular epithelium are not unknown. They are frequently stated to be rare, but are probably often overlooked. I have seen large goblet cells distended with mucin in the gall-bladder of a case of cholecystitis. Schridde<sup>44</sup> records their presence in the endometrium in chronic inflammatory conditions.

*Conclusions.*—(1) The normoplasia of an epithelium, the extent to which its differentiation proceeds at a given spot, is fixed. In pathological conditions it can, however, be exceeded. It now tends to approach the maximum of differentiation possible. Prosoplasia of the epithelium sets in.

(2) Fig. 9 demonstrates that all the layers of an epithelium

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take part in this progressive change. It begins in the basal cells, and a typical "epidermal" epithelium results.

(3) The fundamental tissue-characters of the epithelium remain unchanged. In this respect prosoplasias differ from metaplasias.

(4) Prosoplastic changes can occur at every period of the life of the individual. Herein they differ from heteroplasias. Their exciting cause is of the nature of a stimulation by chronic inflammations and suppurations.

(5) The manner in which these stimuli act is obvious in most cases. On surfaces lined by squamous epithelium a tough layer of horn is formed, which protects the delicate cells of the mucous membrane and of the mesenchyme from contact with irritating secretions, etc. The same purpose is served in columnar epithelia by the production of mucin by goblet cells.

(6) Since differentiation in excess of the normal degree is possible, it follows that the normoplasia of an epithelium is not a fundamental property of its cells. It depends solely on their environment, on the nature of the stimuli to which they are exposed.

### IV. HETEROTOPIC DIFFERENTIATION

Under this heading I include several observations, which probably differ widely in the manner of their production. I might, with equal justice, have placed them with the heteroplasias, the prosoplasias, and the metaplasias. As they appear to form connecting links between these conditions, this is the most appropriate place in which to discuss them. I have used the non-committal term "heterotopic" in the heading to this paragraph, since the tissues they contain are certainly "out of place."

*Squamous Epithelium in Infundibular Process of Pituitary* (Fig. 10).<sup>\*</sup>—Erdheim<sup>9</sup> was the first to point out that islands of squamous epithelium are frequently found in this region in elderly subjects. Fig. 10 illustrates the best instance of their presence that I have seen. It was taken from the pituitary of a woman of sixty-eight, who had died of osteitis deformans. The infundibular process contains more fibrous tissue than usual. Small epithelial cells, grouped to form acini, are scattered about in the stroma. They are slightly smaller than, but otherwise identical in structure with, the clear cells of the anterior lobe of the gland. Some of these acini, however,

<sup>\*</sup> For the specimen from which this drawing has been made I am indebted to Dr. J. R. Perdrau, of the Lambeth Infirmary.

contain larger cells, that stain more intensely. In the smallest acini in which they are present, they are mostly cylindrical and elongated, and correspond to the basal cells of squamous epithelium. They increase in number and differentiate into rounded and polygonal cells, many of which possess faint intracellular fibrils and distinct prickles. Cell nests are formed, whose centres consist of large swollen elements, that retain their nuclei and show no evidence of keratinisation. It is obvious, from a study of the sections, that all the squamous cell nests have developed within acini that have enlarged with their growth. A few of the smaller acini contain one or two pituitary cells among their squamous contents.

The anomalous fact of the presence of squamous epithelium

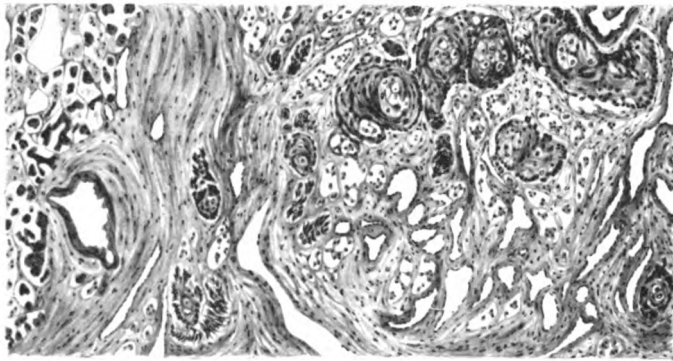


FIG. 10.

Heterotopic squamous epithelium in infundibular process of pituitary.

within the cranial cavity becomes less so when the development of the pituitary is remembered. Its anterior lobe, together with the infundibular process, of which it is a part, is developed from the ectodermal epithelium of the buccal cavity, which grows upwards as the pituitary duct, near the apex of which the anterior lobe of this organ is differentiated out of its cells.

The islands of squamous epithelium figured above are thus seen to correspond to that of the buccal cavity. The degree of differentiation of the two is identical, since keratinisation is absent in both. Their presence can be accounted for in two ways. On the one hand, certain cells remain in an undifferentiated condition for years, and then undergo differentiation, not in the direction that is the dominant one for the part, but in the alternative direction, the one which the epithelium of the buccal cavity, the organ nearest in position to it, undergoes

normally. On this assumption they represent a belated heteroplasia. On the other hand, it is possible that differentiated cells of the infundibular process have given up their tissue character, and assumed that of the buccal epithelium. If this be the true explanation, we have a metaplasia in this case.

I cannot decide which of these explanations is the correct one, since it is impossible, from the appearance of the basal cells of these islands, to tell their history. But I must confess that I am no believer in the persistence for many years of undifferentiated cells in an "embryonic" condition, an article of faith that forms the foundation of the most generally accepted theory of tumour formation. All the evidence we possess indicates that cells that have lagged behind in their development either complete it shortly after the other cells of the tissue, or else are destroyed and disappear.

Whatever be the exact manner of formation of this heterotopia, it is of interest in that it shows that, even late in life, a recessive character can take the place of the dominant one in an epithelium. It strengthens the view that the structure of the cells of an organ is not so much an inherent constitutional necessity, as the result of their position in the body and of the action of stimuli outside them. The nature of the stimulus that is responsible for the change observed in the present instance is quite obscure. All that can be said about it is that it becomes more frequent with advancing age. Lubarsch,<sup>24</sup> however, describes squamous cell nests and atheromatous cavities in the stalk of the pituitary of infants.

The following observations concern tissues the zenith of whose development is attained at some period of embryonic life. The first deals with an organ that usually persists in a rudimentary condition. The others concern structures that disappear completely during later development, but occasionally fail to do so. They then undergo differentiation into tissues which are normally found in other parts of the organic system to which they belong. I propose to do no more than draw attention to these conditions. Attempts at their explanation must be deferred until more instances will have been recorded, since little more than speculations as to the manner of their formation can be indulged in at the present time.

*Wolffian Remains in the Female.*—The parovarium persists as a series of tubules in the mesovarium and the mesosalpinx. Its developmental significance and homologues in the opposite sex have been worked out by Ballantyne and Williams.<sup>5</sup> It varies considerably in size and extent in different individuals.

Its tubules are lined by a single layer of cubical or columnar epithelium and are surrounded by irregular bands of fibromuscular tissue, that spread out to join the surrounding vessels and strands of areolar tissue.

It should be noted that the epithelium has undergone differentiation, and that its cells present none of the appearances of young embryonic cells. This observation applies to all the "embryonic rests" I have examined.

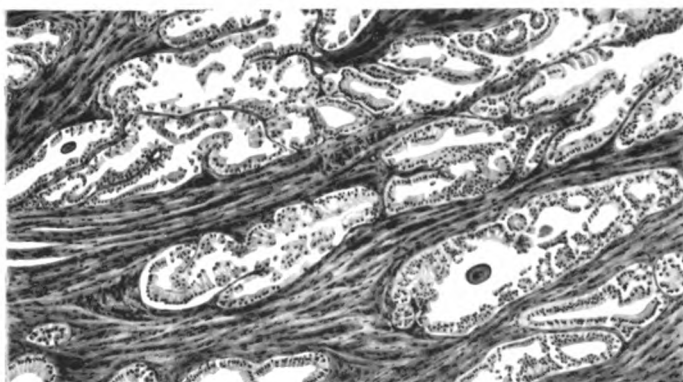
Beyond a tendency to slight dilatation owing to accumulation of albuminous hyaline secretion these organs appear to undergo no appreciable changes with advancing age. Occasionally, however, changes are observed in them.

In a parovarium, the majority of whose tubules had been converted into small cysts, I found two flattened and slightly compressed tubules, both of which are lined by non-keratinised squamous epithelium. This change was first described by Meyer,<sup>29</sup> who regarded these cells as derivatives of the epiblast, that had been incorporated with the Wolffian body during the early stages of its development. Later, however, he<sup>30</sup> retracted this view, and now considers them to represent modifications of the parovarian epithelium. With the latter view I agree. Whether this epithelium has been produced by metaplasia, as Meyer suggests, or by prosoplasia, I cannot decide. It is clearly comparable with the squamous cell nests in the infundibular process of the pituitary.

Unobliterated vestiges of Gaertner's duct are lined by cubical, columnar, or by squamous epithelium.

*Prostatic Tissue in the Urachus* (Fig. 11.)—At the post-mortem examination of a man of forty-seven, who had died of chronic heart disease, the unobliterated lower end of the urachus, immediately above the apex of the bladder, was found to be occupied by an oval tumour, 5.7 cm. in length by 4 cm. antero-posteriorly. It is surrounded by a fibrous capsule, is firm in consistency and is occupied by a number of cysts, that vary much in size. Microscopically it consists of tubules and spaces, which are dilated to form the cysts, and are lined by an irregular cubical or columnar epithelium. The lumina often contain typical small corpora amylacea. The stroma is composed of dense fibro-muscular tissue. It projects into the glandular spaces as papillæ that are often branched. The figure shows that, without doubt, the structure of the tissue is identical with that of the prostate. The epithelium is hyperplastic, and the resemblance to certain hypertrophies of this gland is very close indeed. The prostate itself is without abnormality.

Glands, identical with those of the prostate are commonly found under the mucous membrane of the prostatic part of the urethra, as well as at the neck of the bladder in both sexes. Jores<sup>19</sup> has shown that the formation of the middle lobe in enlargements of the prostate depends on the hyperplasia of the latter group of glands. I have myself observed down-growths of urethral epithelium and their conversion into prostatic glands in hypertrophies of this organ. Thorel<sup>48</sup> has described small adenomyomatous proliferations of prostatic glands in the trigone of the bladder, between the orifices of the ureters, in men. Wittzack<sup>52</sup> (ref. Thorel), has seen a similar structure at the junction of the fundus and the posterior wall,



1/10 mm.

FIG. 11.

Prostatic tissue in unobliterated urachus.

beyond the opening of the right ureter, and a considerable distance from the neck of the bladder. His case refers to a male.

Aschoff<sup>4</sup> has studied the mucous membranes of the urinary tract, and concludes that all the glands of the urethra in either sex, as well as those that make their appearance in the renal pelvis, the ureter and the bladder in inflammatory conditions, are of the nature of prostatic glands.

The only case that I know of that is comparable with the one under consideration, has been recorded by v. Luschka.<sup>25</sup> In a man of nineteen he found a sinus lined by squamous epithelium on the dorsal aspect of the root of the penis, into the proximal end of which there opened a lobulated gland, whose structure and secretion were identical with those of the prostate. He explains it as the displaced anterior median lobe of that organ. Meyer<sup>33</sup> (p. 623), however, points out that the

sinus is in all probability a remnant of the cloacal membrane that has failed to involute, and has undergone differentiation into glands which conform with those that normally arise from the cloacal epithelium. v. Luschka's case is thus strictly comparable with the present one, since they both consist of prostatic tissue that has arisen in a part of the cloaca that normally disappears completely.

On summarising these brief abstracts from the literature and on comparing them with the tissue found in the urachus, the following conclusions appear to be justified. All the normal glands of the cloaca, as well as those that are formed in pathological conditions, are of one type, namely, prostatic glands. Should parts of the cloaca that disappear during later development fail to do so, they are able to undergo differentiation into identical glands. This potentiality does not reside exclusively in the endodermal cloaca, but is shared by that part of the mesodermal Wolffian duct that forms the trigone of the bladder and gives off the ureter.

These facts point to the interesting conclusion that the urachus and the other purely temporary parts of the cloaca disappear from causes outside their own cells, and not for intrinsic reasons, such as old age of their tissues. Not only are these cells able to persist, but at the time when they usually disappear they contain the same prospective potentialities as those of the permanent parts of the cloaca. Since the cloaca gives rise to one kind of gland only, it will not be amiss to compare it with another part of the endoderm in which disappearance of one segment usually takes place during development, whereas the other undergoes differentiation in several directions.

*The Vitelline Duct.*—This structure occasionally fails to become obliterated throughout the whole or a part of its length. If it persists at the umbilicus, it soon becomes more or less extroverted and a so-called umbilical polypus results. Its unobliterated proximal end forms a Meckel's diverticulum. All parts of the patent duct are usually lined by a mucous membrane that is identical in structure with that of the ileum. In rare cases, however, glands typical of other parts of the intestinal canal are found in its remnants. Pyloric glands have been recorded in an umbilical polypus by Tillmanns.<sup>49</sup> \* Cardiac glands were found in the umbilical part of a patent vitelline duct by Salzer,<sup>40</sup> and at the apex of a Meckel's diverticulum by Meulengracht.<sup>28</sup> The latter specimen contained typical chief and oxyntic cells. Brunner's glands are described by

\* I have recently been given a similar specimen by Mr. A. Todd, who removed it from a young infant.

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Kern<sup>21</sup> in the extroverted distal end of a patent duct, and by Tschiknawerow<sup>50</sup> at the apex of a Meckel's diverticulum. Wright<sup>53</sup> (ref. Reitmann) found a small encapsulated pancreas with typical islands of Langerhans in the subcutaneous tissue of the umbilicus of a girl of twelve, and Albrecht and Arzt<sup>2</sup> saw an equally typical pancreas in the wall of a true Meckel's diverticulum.

The epithelium of the vitelline duct, when it persists abnormally, shares with that of the stomach and small intestine the potentiality to form pancreatic tissue. Whereas the proximal part of its mucous membrane always undergoes differentiation in the direction of that of the ileum, its distal part is able to give rise to cardiac, pyloric and duodenal glands. We have seen that the heteroplasias of the intestine always represent the tissue character of the segment next to the one in which they occur. Contrary to what might have been expected, the epithelium of the duct possesses wider prospective potentialities than that of any part of the permanent intestine. This apparent anomaly is, however, explained by its developmental history.

The vitelline duct is, at first, a very wide opening, almost as wide as the whole of the primitive gut. On account mainly of the growth of the embryo, it is rapidly reduced in width and, according to Lewis,<sup>22</sup> is detached and obliterated in embryos of from 5 to 7 mm., long before the intestinal epithelium shows the least signs of differentiation. This author states that, in the stomach, epithelial pits first make their appearance in 16 to 19 mm. embryos, and solid buds of granular cells, the first rudiments of the gastric glands, at 99 mm. In the small intestine the development of villi begins, in its upper part, at 19 mm., they spread downwards and are found throughout its whole length only at the 130 mm. stage. Lieberkuhn's glands first appear near the pylorus at 78 mm. At 120 mm. they have reached the middle part of the small intestine.

Whereas the vitelline duct normally disappears during the first month of embryonic life, differentiation of the glands of the intestine does not begin until towards the end of the fourth month.

There is no reason to suppose that the epithelium of the vitelline duct, at the time that it is almost as wide as the primitive gut, does not share in all its prospective potentialities, or that it fails to retain them until the time of its disappearance. If the view is correct that differentiation and development are essentially reactions to unequal stimulation, it follows that every part of the gut must, during the whole of its



subsequent existence, constantly be undergoing differentiation in different directions, until its permanent characters are attained, since no two parts of it are subjected to precisely the same environmental conditions. If every stage of development is, as I have said above, a parting of the ways, different characters constantly become dominant in different segments, the other original potentialities at the same time becoming recessive.

But if the vitelline duct persist abnormally, its proximal end will be subjected to the same conditions as the loop of small intestine to which it is joined. This part of Meckel's diverticulum has therefore always the structure of the ileum, and shares with it (and with the rest of the duct) the potentiality to produce pancreatic tissue. The distal part of the duct, especially if it be constricted or isolated, is much more independent of natural environment. Here the conditions are grossly abnormal as compared with the rest of the intestine, and all the prospective potentialities of the duct can be, and actually are, unfolded. Precisely why it should in one case produce gastric and in another duodenal glands it is impossible even to guess. But I believe that these differences in structure depend on differences in stimulation. The generally accepted view is that, when cells are displaced from their natural surroundings, they remain "embryonic" and less differentiated and their potentialities are therefore abnormally great. I believe that the potentialities are identical in all the cells of the fore-gut and of the vitelline duct. They require external stimuli to become developed. Where these stimuli are most varied, there the greatest number of the primitive potentialities will have the best chance of being unfolded.

I know of but one observation in the embryo that concerns this question. Siegenbeek van Heukelom <sup>46</sup> has described a nine-months fœtus with a Meckel's diverticulum with the structure of the small intestine, and an isolated umbilical polypus with that of the pylorus of the same individual. This observation indicates that the persistent remains of the vitelline duct undergo their development *pari passu* with that of the intestinal canal. It tends to support the view that these heterotopic glands are not the result of the persistence of the epithelium in an embryonic condition.

## V. HETEROTOPIC BONE FORMATION

Bone is frequently deposited around and upon foci of calcified necrotic tissue. The commonness of its occurrence

can be judged of from the writings of Pollack,<sup>38</sup> who found it in over 70 per cent. of the calcareous lymph glands he examined.

Bone occurs most frequently in old tuberculous lesions, since the caseous areas that result from the action of the tubercle bacillus are very liable to undergo calcification. I have seen it in calcified scars of the lungs on several occasions.

Next in frequency this tissue is found in arteries that are the seat of arterio-sclerosis. Its usual site is the media, where it surrounds and replaces the calcareous plaques characteristic of the later stages of this affection. I possess sections of a large calcified aneurysm of the profunda femoris artery, the greater part of whose wall consists of branched and anastomosing trabeculæ of laminated bone, many of which are surrounded by osteoblasts and contain well-marked Haversian canals. They are embedded in a vascular gelatinous marrow with numerous fat cells.

The veins are more rarely the seat of bone formation than are the arteries. I have seen a large vein in the substance of the liver, whose lumen is filled by a calcified thrombus, at one end of which there are a few trabeculæ of conspicuously laminated bone. They are embedded in a delicate gelatinous marrow with a few small groups of myelocytes close to its wide thin-walled capillaries.

In the heart bone can be found occasionally in calcified vegetations and sclerotic patches of the valves and other parts of the endocardium. Fig. 12 is a drawing of the lymphoid marrow surrounding the spicules of bone in a calcified patch in the left auricle. It shows large fat cells and wide blood spaces, as well as numerous groups of erythroblasts and myelocytes, among which megakaryocytes are conspicuous objects.

Bone has been found in the skin and subcutaneous tissue, usually in association with calcified sebaceous cysts and epitheliomata. I have seen a spicule of laminated bone among the hair follicles of the subcutaneous tissue of the lower lip. It is bent to form an almost complete circle. The narrow interval between its ends lies on its deep aspect and is occupied by a group of sweat glands. Its concavity is filled with adipose tissue that does not differ from the neighbouring lobules of subcutaneous fat. Its convexity is surrounded by bundles of areolar tissue. There are no indications of its causation; it was found by accident.

I have found small spicules of osteoid tissue and bone in the sclerosed fibrous tissue under the granulations lining an artificial anus of about a year's standing. There are no signs of necrosis or calcification of the surrounding fibrous tissue, whose cells have proliferated and enlarged in places. These large connective tissue corpuscles are identical in structure with osteoblasts. They form small irregular groups. Osteoid

tissue appears between the cells, some of which are enclosed within it as bone corpuscles. Calcification rapidly supervenes and narrow irregular spicules of bone result. The appearances are the same as those described by Busse,<sup>7</sup> who draws attention to the rare cases of ossification of inflammatory tissue without antecedent necrosis or calcification.

The majority of the specimens enumerated above contain evidence of absorption and moulding of the bone. Multi-nucleated giant cells are frequently found within lacunæ on the surface of the trabeculæ.

Bone has been produced experimentally. An especially favourable tissue for its study is the rabbit's kidney. The most recent paper on this subject is one by Asami and Dock.<sup>3</sup>

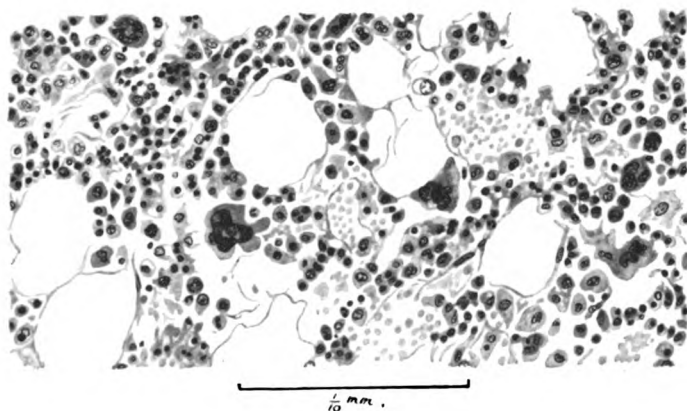


FIG. 12.

Lymphoid marrow in heterotopic bone in left auricle.

It will be seen from the above list that heterotopic bone formation occurs in many parts of the body. Indeed there is no tissue in which it cannot take place in suitable conditions. These conditions are fulfilled, in the vast majority of cases, when a necrosis has undergone calcification.

A few years ago I<sup>35</sup> described the changes that led to bone formation in a necrotic calcified epithelioma of the skin, which was particularly favourable for their study. Since then I have had the opportunity to examine another case of the same kind. I need do no more than give a summary of the conclusions that I arrived at.

The dead calcified epithelium of the tumour takes no active part in the formation of the bone. Just as every other calcareous focus, it acts merely as a scaffolding, on to which the bone is deposited (Fig. 13). In this respect it performs the same function as cartilage in endochondral ossification.

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The calcified tissue acts as an aseptic irritant, and induces a mild degree of plastic inflammation of the neighbouring connective tissue. The latter reacts to it in the usual manner, its fibroblasts divide and multiply, and give rise to cellular granulation tissue, with numerous capillary vessels, which surrounds the calcareous plaques.

Like every other insoluble foreign body, the calcified tissue is eroded by large multinucleated giant cells (Fig. 13), that appear to originate from the fibroblasts by confluence or incomplete division, and are to be seen in lacunæ that they have made

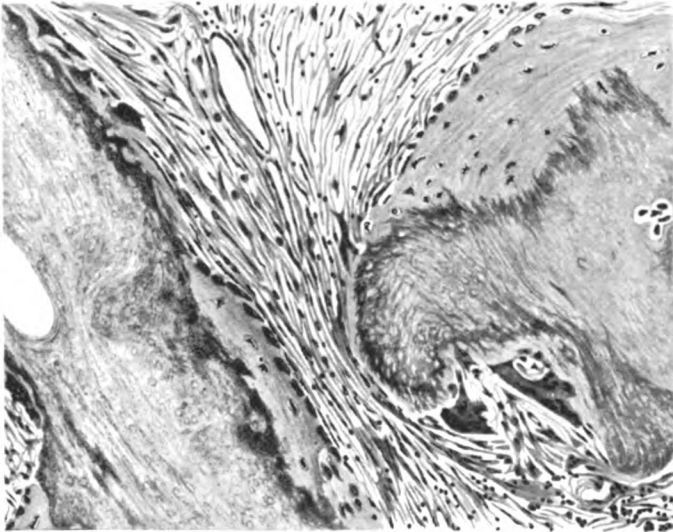


FIG. 13.

Bone formation in calcified necrotic cutaneous epithelioma.

for themselves at its edges. The giant cells display a double activity. They dissolve the Calcium salts by means of the  $\text{CO}_2$  produced by their active metabolism, and then liquefy the organic remains by means probably of extra-cellular ferments. Such fragments as resist liquefaction they surround and ingest, and eventually digest them completely.

The fibroblasts that immediately surround the calcified tissue react to the local supersaturation with the Calcium salts dissolved by the giant cells in the same manner as when they come into contact with calcified cartilage during normal ossification. They take on the functions of osteoblasts, and often their shape as well (Fig. 13), although the latter phenomenon is not an invariable and necessary one. Instead of laying down the

matrix of fibrous tissue, they lay down that of laminated bone. Some of them are surrounded by its fibres, thus becoming bone corpuscles with typical branched processes which extend within the canaliculi of the matrix.

Once bone has been laid down it extends into the calcified tissue by means of "invisible absorption" of its constituents in the manner I have attempted to explain in my paper on the subject. The necrotic tissue is eventually replaced completely by it. No sooner has the bone been formed than it begins to be reabsorbed by osteoclasts. The absorption progresses until the whole of the newly-formed bone may disappear, and nothing remains but a fibrous scar.

The process described above appears to be a peculiarly purposive adaptation to alterations of environment. Calcified tissue is highly insoluble, its removal takes a long time. It seems to be much easier and quicker for the body to react by the formation of bone, a calcified living tissue, which surrounds and eventually replaces the dead foreign body. That this is, so to speak, the reason of its production, is shown by experimental evidence. The longer the animals are kept alive, the more marked are the signs of reabsorption. Thus Maximow<sup>27</sup> found traces only of bone at the end of a year.

No sooner has bone been deposited than the granulation tissue surrounding it acquires the characters, first of gelatinous, next of fatty, and lastly of lymphoid marrow. A striking example of the latter, in which there is abundant evidence of hæmopoiesis, is afforded by the calcified plaque from the left auricle illustrated in Fig. 12. I have seen a supra-renal, the centre of which had been replaced by fatty and lymphoid marrow. I attribute its presence to calcification, the result of hæmorrhage or of necrosis. The calcified material had been substituted by bone, which had been completely reabsorbed, the marrow only remaining.

The fate of the cartilage of the developing skeleton, except where it forms the articular surfaces of joints, is to die and to become calcified, forming a scaffolding on which bone is deposited by the fibroblasts of the vascular connective tissue by which it is invaded. Thus, it is produced throughout life under the periosteum whenever a very abundant callus is formed. Kapsammer<sup>20</sup> saw it in his experiments with much displacement and movement of the fragments at the site of fractures. I have observed it on several occasions in the shells of bony tissue around cysts of the long bones. Cartilage is a purely temporary structure whose matrix is prone to calcification. As it forms a

very suitable material on which ossification can take place, it makes its appearance when an unusual amount of callus is produced.

Islands of cartilage are occasionally found in heterotopic bone formation. This tissue has been produced experimentally on several occasions, for instance by Harvey<sup>13</sup> in the rabbit's aorta. In man it has been found with some regularity in laparotomy scars. Strassberg<sup>47</sup> saw it two months and a half after an operation. Fig. 14 represents a part of a nodule, 2 cm. in length by  $\frac{1}{2}$  cm. in thickness, which was found in a scar in the falciform ligament of the liver immediately above the umbilicus of a man of forty-seven, on the forty-first day after

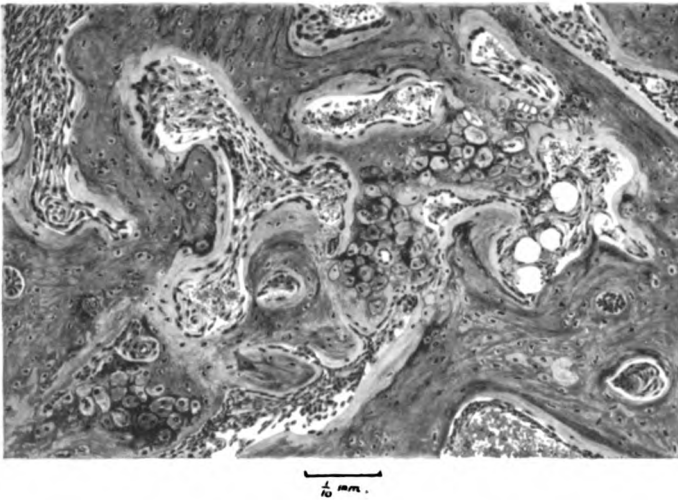


FIG. 14.

Cartilage and bone in calcified scar, forty-one days after laparotomy.

an exploratory laparotomy. It was firmly calcified and is seen to consist of branched trabeculae of lamellar bone, with Haversian canals. The centres of many of the trabeculae contain the remains of a calcified hyaline cartilage, which is being replaced by bone. In one part of the specimen there is a large nodule of cartilage, whose formation from the surrounding cellular connective tissue is shown in Fig. 15. The fibroblasts gradually increase in size, and are arranged in rows owing to the secretion of a hyaline matrix between them, which becomes condensed around them as capsules.

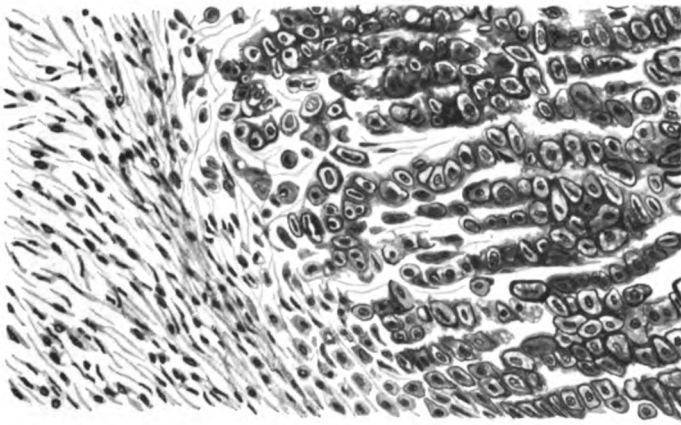
*Conclusions.*—(1) When necrotic calcified tissue, because of its irritant action, is surrounded by cellular granulation tissue, the fibroblasts of the latter readily take on the functions, as

well as the structure, of osteoblasts and deposit layers of laminated bone on its surface.

(2) This change in the fibroblasts is due to stimulation by the local excess of Calcium salts dissolved out of the calcified tissue by the action of foreign body giant cells, and probably of the fibroblasts themselves.

(3) This alteration of function is susceptible of one of two explanations :

- (a) The fibroblasts change their character. Instead of remaining fibroblasts and producing fibrous tissue, they undergo a metamorphosis into osteoblasts and produce bone. The change is a direct metaplasia. The cells



$\frac{1}{10}$  mm.

FIG. 15.

Formation of hyaline cartilage from connective tissue of same specimen.

that have undergone differentiation in one direction lose it, and undergo differentiation in another direction.

- (b) Fibroblasts are, to all intents and purposes, undifferentiated. The function that is performed by them at a given moment depends solely on the stimuli to which they are subjected. When these change, the functions alter. In the absence of Calcium salts in solution, the various forms of areolar and fibrous tissue are produced according to circumstances. In their presence in sufficient concentration bone is laid down. The change of function is not due to an alteration of the character of the cells; it is a reaction to an alteration of the environment.

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I have attempted to show elsewhere<sup>35</sup> that the second explanation is the correct one. Fibroblasts, especially when they are in a state of active proliferation, resemble very closely indeed the cells of the primitive mesenchyme. They are indifferent cells, that readily give rise to every kind of areolar and fibrous tissue. Since the organic matrix of bone is very similar to that of connective tissue, no fundamental change is required in the cells that deposit it.

(4) When much new bone is produced rapidly, the periosteum of the skeleton forms cartilage as an intermediate tissue that can easily be replaced by bone. The fibroblasts in general share this ability, and hyaline cartilage is occasionally found in heterotopic bone formation.

(5) The heterotopic ossifications afford us instances of the fact that, within the group of the connective tissues, the exact nature of the structure produced does not depend on the character of its cells, but on the stimuli to which they are subjected. They illustrate the amount of "regulation" that can take place in the adult body. They suggest that the cells of the skeleton do not differ in their essential characters from those of the other connective tissues.

(6) They can often be examined in an unfinished condition, and their mode of origin thus investigated. They strengthen the view that the epithelial heteroplasias and allied anomalies have an analogous causation, and that differentiation and development are, in great part, reactions to stimuli from outside the cells themselves.

### VI. THE METAPLASIAS OF EPITHELIUM

In inflammations, especially when they are suppurative and of a subacute or chronic nature, surfaces that are naturally lined by columnar cells are occasionally found to be covered by squamous epithelium. These lesions are always characterised by a considerable amount of proliferation and new formation of the fixed cells of the part. They constantly react to the injury and attempt to repair the losses produced by it. The ultimate result depends on the nature and strength of the irritant. If the tissues cannot react to it they die, and necrosis and ulceration result. But reaction takes place to less powerful irritants. The connective tissue proliferates and gives rise to vascular granulation tissue. The epithelium at the edges of the lesion and the parts of it that have escaped destruction within it, also proliferate and constantly tend to spread on the surface of the naked granulations and to cover them. As soon as the inflam-



mation abates to a sufficient extent the epithelial covering is restored.

In some cases this covering becomes squamous instead of columnar. It must be remembered that such a change is much more than one of form, since it demands the loss of the power to produce mucin, cilia, etc., and the acquisition of a new set of characters, namely intra-cellular fibrils, prickles, and the ability to keratinise. To this change the name of "metaplasia" has been applied.

Before I attempt to offer an explanation of this phenomenon, it will be advisable to give a list of some of the epithelial metaplasias that are known to occur.

There are two parts of the body where, in my experience, a metaplasia of columnar into squamous epithelium takes place with some degree of frequency in chronic inflammations, and where it is possible sometimes, from the histological appearances, to form conclusions as to the manner in which it has been developed. Both these places are close to regions that are lined by squamous epithelium. One is the respiratory part of the nose and the air sinuses that communicate with it. They are lined by a ciliated columnar "respiratory" epithelium, a derivative of the epiblast. The other is the cervical canal of the uterus, whose covering consists of a columnar mesoblastic epithelium. The inflammatory polypi that are commonly found at these spots are often lined by squamous as well as by columnar cells.

About 50 per cent. of the nasal polypi I have seen possess a partial squamous covering. Schridde<sup>45</sup> has described and illustrated their microscopic appearances. I can corroborate his statements, to which I have nothing to add. I have examined large inflammatory granulations from the maxillary antrum. Many of them are covered by a beautiful squamous epithelium showing faint traces of keratinisation. The prickly cells are very well developed. In places where the epithelium is œdematous these cells have been forced apart by fluid. Here their connecting processes are often greatly elongated and stretch from cell to cell across the intervening space.

Analogous appearances can be observed in the polypi that arise in the cervical canal. They consist of lobulated masses of inflammatory granulation tissue. In some specimens all stages from loops of young blood-vessels surrounded by leucocytes to differentiated fibrous tissue can be traced. A part of one of these polypi is represented in Fig. 16. Pieces of two contiguous lobules are to be seen, built up of vascular young connective tissue. The larger is lined by squamous epithelium on its external surface. The space between the lobules, which ends blindly beyond the limits of the drawing, is covered in its

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deeper part below by a row of columnar cells with small deeply stained oval nuclei and clear free extremities. They present all the features of young cervical epithelium. Between them and the squamous covering there is a band of a single layer of large irregular cells devoid of definite characters, with big faintly stained vesicular nuclei, that merge on the one side with the cells of the squamous epithelium, and on the other with those of the columnar kind. As soon as the latter acquire a certain degree of differentiation, the superficial part of the connective tissue on which they rest becomes condensed to form a basement membrane for them. This is completely absent under the squamous epithelium. Identical pictures are found again and again in all parts of the specimen. They can only

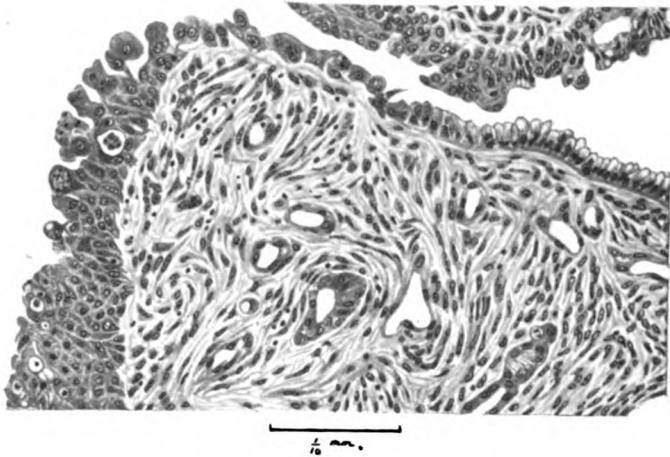


FIG. 16.

Metaplasia of epithelium of polypus of cervix uteri. Indifferent cells giving rise to squamous epithelium on the one side and to cervical epithelium on the other.

be explained on the assumption that the zone of cells in the middle gives rise to squamous epithelium on the surface of the polypus, and to cervical glands in its sheltered bays.

These polypi represent a large increase in the surface of the cervical canal, that is covered by its epithelium as soon as circumstances permit. In order to accomplish this its cells have to proliferate to an enormous extent, and in so doing they exhibit no tendency to become columnar. They glide over the surface of the mass of granulations and into all its exposed tissue spaces as rounded and irregular large cells identical with those seen in Fig. 16. The youngest granulations are always covered by them. Not until they have been covered do the cells of the epithelium stop their rapid division and begin to differentiate. They now possess the potentiality to do so in two directions. On the surface of the polypus they produce

squamous epithelium, and in its narrow tissue spaces they give rise to cervical glands.

Fig. 16 proves that this is not a replacement of cervical glands by squamous epithelium, islands of which have been shown by Meyer <sup>31</sup> to persist under the columnar cells of the cervical canal. I am familiar with this replacement in erosions of the cervix, which are healing ulcers covered partly by the squamous epithelium of the external os, and partly by the columnar mucous membrane of the canal. A continuous struggle goes on between these cells, on the issue of which the nature of the ultimate covering of the lesion depends. The cells of one epithelium insinuate themselves under those of the other, lifting them from the connective tissue and thus separating them from their blood-supply. This struggle is going on to a slight extent in the upper lobule in Fig. 16. Some compressed columnar cervical glands have here been pushed by a layer of young squamous epithelium into the lumen of the space in the left-hand corner of the figure.

Observations like this show that the columnar epithelium of certain parts of the body, after long-continued proliferation, during which the appearance of its cells warrants the conclusion that it has lost a part at least of its differentiation, can revert to a primitive condition and undergo heterotopic differentiation into squamous epithelium. At the same time it retains the power to produce columnar cells.

The epithelium of the ducts of the salivary glands occasionally undergoes identical changes. I have seen a case of suppuration of the submaxillary, whose ducts, where they are surrounded by young granulation tissue, possess a partial lining of squamous epithelium with numerous mitoses. It occurs as islands that are easily recognisable by the size of the cells and the shape of the nuclei. They are always connected with the basal layer of the cells of the duct, and have pushed its columnar epithelium into the lumen and caused it to become loosened and desquamated in many places. In a case of chronic suppuration and fibrosis of the parotid that I have examined, the greater part of the gland has been converted into dense fibrous tissue, between the strands of which a few atrophied and inflamed secreting acini remain. In many parts of the sections there are irregular, often branched, strands and islands of squamous epithelium, with well-marked columnar basal cells. Many of these islands bear a striking resemblance to the epithelium of the vagina, their central cells being swollen, with pale bodies surrounded by deeply stained "cell membranes."

McKenzie <sup>28</sup> found an extensive metaplasia into squamous epithelium in the smaller bronchi of four cases of broncho-pneumonia in children, out of a total of forty-three cases

examined. I have seen these changes on several occasions. They are very rare in adults, but the best instance I have observed is from a man of forty, who had died of a sub-acute form of this affection. Some of the small bronchi are completely lined by squamous epithelium with distinct prickles, and with numerous minute globules of keratohyalin in its superficial cells. The lumina are often occupied by desquamated shreds and bands of ciliated epithelium.

I have seen the vas deferens lined by squamous epithelium with slight keratinisation in a case of tuberculosis of the epididymis. Its wall is thickened and infiltrated with lymphocytes. In two instances of this disease I have found squamous epithelium lining some of the tubules of the epididymis. It is surrounded by tuberculous granulation tissue in both cases, and exhibits a marked tendency to form branched papillæ that grow outwards into it. Keratinisation is present in one of them only.

Metaplasias into squamous epithelium as a result of inflammation are extremely rare in the alimentary tract. It is of interest to note that Fütterer<sup>12</sup> found it twice in gastric ulcers that he had produced experimentally in rabbits. The only instance of its presence in the gall-bladder in man that I know of has been recorded by Lubarsch,<sup>23</sup> who found a strip of squamous epithelium in a case of cholecystitis with gall-stones at the base of a small inflammatory granuloma.

It is not my intention to do more than mention the relative frequency with which squamous epithelium is found in carcinomata that arise in mucous membranes and organs lined by columnar epithelium. Its presence has been recorded in nearly all parts of the body. In my experience it is to be found in about 50 per cent. of the carcinomata of the corpus uteri. Herxheimer<sup>16</sup> has described a series of cases comprising the gall-bladder, stomach, cœcum, pancreas and the uterus. It is worthy of note that, in marked contrast to the extreme rarity with which squamous epithelium has been found in inflammations of the gall-bladder, this organ is rather frequently the site of a squamous carcinoma.

It will be seen from the foregoing observations that squamous epithelium has been found in association with the proliferation of chronic inflammation and in malignant tumours in a variety of places that are normally lined by columnar-celled mucous membranes. In accordance with what one would expect, it is met with in regions close to surfaces covered with squamous cells with comparatively great frequency. Here its method of formation from the proliferated cells of the part can occasionally be studied (*cf.* Fig. 16). Heterotopic squamous epithelium

becomes much rarer in internal organs and, in many localities, has never yet been found except in carcinomata.

All the instances hitherto enumerated concern conducting surfaces, the bronchi, the gall-bladder, etc., or the ducts of glands. Thus, in the two cases in which squamous epithelium was found in the salivary glands it was limited to the ducts. Since the cells of these structures are obviously much less highly differentiated than those of the secreting acini, and since they alone, in many cases, retain the power to proliferate (Schaper and Cohen <sup>42</sup>), it follows that, when metaplasia occurs, it is almost exclusively confined to the epithelium of the ducts.

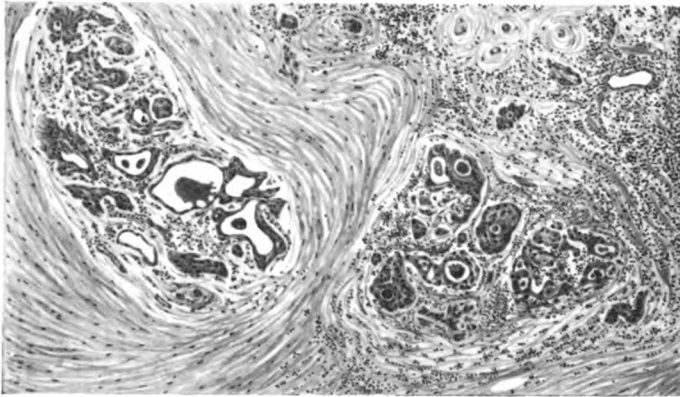


FIG. 17.

Metaplasia of epithelium of thyroid in myxœdema. The atrophied vesicles, some of which contain remnants of colloid, are lined by squamous epithelium.

In fact, I have been unable to find a single record of the metaplasia of glandular epithelium. The following case is therefore of great interest, since it is, to the best of my knowledge, the first instance of the conversion of a highly differentiated secreting epithelium into cells of the squamous type.\*

The specimen is a thyroid, which has undergone a uniform and extreme diminution in size, although its shape has been retained. Its surface is slightly granular, it is pale in colour and tough in consistency. Its lateral lobes measure about 15 mm. in their longest diameter. It was found at the post-mortem examination of a woman of fifty-four, who had suffered from severe symptoms of myxœdema for four years.

Microscopic examination shows that the whole of the organ

\* Squamous-celled carcinomata of the thyroid, of which I have seen instances, have been recorded.

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has been replaced by a dense acellular fibrous tissue with very thick-walled blood-vessels. Scattered between the fibrous bundles are the remains of epithelial alveoli (Fig. 17). They are surrounded by rings of cellular granulation tissue densely infiltrated with lymphocytes, among which numerous fibroblasts and young connective tissue fibrils are found. The epithelium occurs in groups, as solid rods and islands, and as small alveoli, some of which are filled with colloid. All the alveoli are very minute, and are surrounded by a layer of flattened epithelial cells. The whole of the epithelium appears to be squamous, since prickles are present in nearly every alveolus. Fig. 18 is a high-power drawing of three solid masses of epithelium, in many of whose cells distinct fibrillation can be made out.

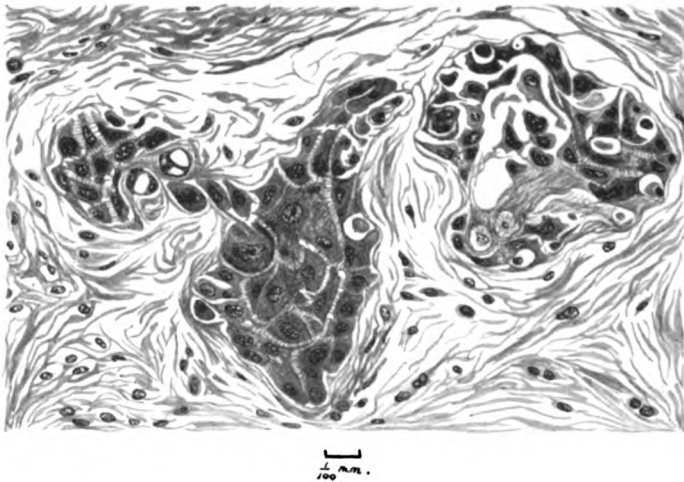


FIG. 18.

Part of same specimen highly magnified. Prickles and intracellular fibrils.

These fibrils pass from cell to cell as very evident bridges or prickles. There are no signs of keratinisation. (The figure shows invasion of the epithelium by connective tissue fibrils, which surround its cells and cause them to degenerate.)

In this atrophied and inflamed thyroid the whole of the secreting epithelium has been converted into non-keratinised squamous cells with fibrillation and prickles. That this tissue represents the original secreting epithelium is proved by the alveolar structure, and by the presence of the last remnants of the thyroid colloid within the lumina of the alveoli. The glandular epithelium has assumed the structure of that of the pharyngeal hypoblast, from a bud of which it is developed. The conversion is complete, and nowhere are there signs of

its early stages. But the marked inflammatory and fibrotic changes suggest that they are responsible for its presence.

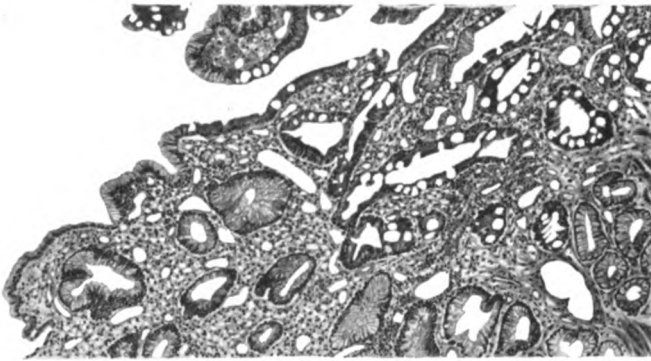
The occurrence of heterotopic squamous epithelium has been demonstrated by a number of instances. The converse metamorphosis is extremely rare. The best instance that I know of is afforded by the tubules lined by columnar epithelium with goblet cells that are found in the deep parts of the mucous membrane of the bladder in cases of ectopia vesicæ. They have been described by Schridde,<sup>45</sup> who shows that they arise from the basal layer of its epithelium. They are comparable with the glands found in the urinary passages in inflammations that have been referred to in the section on "Prostatic tissue in the urachus" (*vide supra*). The same author describes tubular glands with tall cylindrical cells in a non-keratinised squamous carcinoma of the skin. I have seen similar appearances. The deep parts of a basal celled carcinoma (rodent ulcer) of the chin with slight keratinisation, contain numerous irregular branched glands, whose lumina are lined by cubical and columnar cells, many of which are distended with mucin and are typical goblet cells. The explanation of the rarity of the metaplasia of squamous into columnar epithelium probably depends on the reasons given by Schridde.<sup>45</sup> The degree of differentiation is higher in the former than in the latter, and metaplasia is therefore less liable to occur. We have just seen, however, that it can take place in a highly differentiated secreting epithelium. Again, columnar cells on the surface of the body are probably killed as soon as formed by mechanical factors (friction, inflammatory discharges, etc.). It is only in exceptionally sheltered localities, as in the deep parts of tumours, that they can persist.

Very definite changes are found in the epithelium of the alimentary canal in inflammatory conditions. Schmidt<sup>43</sup> was the first to study them systematically in the stomach. He shows that the loss of epithelium that occurs in chronic inflammations and atrophies of the mucous membrane, as well as at the edges of gastric ulcers, is compensated by the cells that have escaped destruction. They often undergo a great amount of proliferation to replace the lost epithelium. In all parts of well over 50 per cent. of the stomachs he carefully examined he was able to demonstrate that the new epithelium assumes the morphological structure of that of the intestine.

The cells of the intestinal epithelium stain deeply, they possess a striated free border, and mucus accumulates in them as true goblets. In the cells of the stomach, on the other hand, the

mucus, or mucigen, is present as irregular small globules between which a delicate cytoplasmic network persists, giving them a finely vacuolated or foamy appearance. It may be added that the nuclei of the goblet cells of the intestine usually retain an oval or rounded form, whereas those of the gastric glands become flattened on the external surface of the cell, often assuming a crescentic shape. The gastric glands are branched, whereas the crypts of Lieberkuehn are not. Brunner's glands of the duodenum agree in these respects with those of the stomach.

I have seen these changes at the edges of ulcers of the pylorus, both simple and carcinomatous, on several occasions. They are to be found at every part of the circumference of the ulcer,



$\frac{1}{10}$  mm.

FIG. 19.

Edge of ulcer of pylorus. The regenerated epithelium covering the granulations has assumed the type of Lieberkuehn's glands.

and extend well above the region of Brunner's glands. One of my specimens shows an absolutely abrupt transition between them and the pyloric glands (Fig. 19). One gland is of the latter kind, the next a crypt of Lieberkuehn, with numerous large goblet cells and a striated "membrane." That all these glands are newly formed is shown by the number of the mitoses they contain, by the irregularity of their shape, and by the fact that they cover young granulation tissue.

Within the last few days I have had occasion to observe changes in the opposite direction in a tuberculous abscess of the vermiform appendix (Fig. 20).

Sinuses are present among the granulations that line it. One of these has acquired a partial covering of epithelium from the nearest intact part of the mucous membrane of the appendix. Glandular down-growths have taken place into the granulation



tissue from the more mature parts of this new covering. One of the glands is branched. Its vertical limb (in the drawing) conforms to the type of a crypt of Lieberkuehn. Its cells are deeply stained and two goblet cells are present near its neck. Contrary to the usual occurrence, their nuclei are flat and crescentic. Two smaller goblets, with oval nuclei, are to be seen at the point where its epithelium joins that of the surface. The other limb of this gland, and all the others that are present, conform to the type of the glands of the upper part of the alimentary canal. In the manner in which their secretion has accumulated as small globules surrounded by strands of cytoplasm, and in which the nuclei become flattened and crescentic, they bear a closer resemblance to the glands of the pylorus than

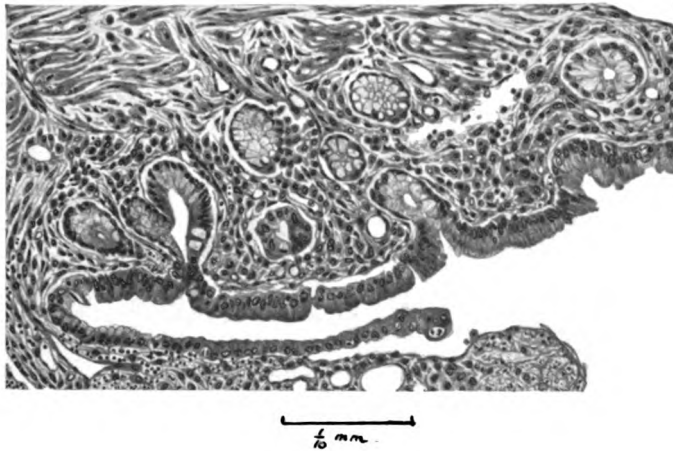


FIG. 20.

Sinus in tuberculous vermiform appendix. The epithelium that has covered it has produced glands of the type of those of the stomach.

to those of Brunner. They are still young and not yet fully matured, but in those in which differentiation is furthest advanced the resemblance to these glands is undeniable.

The specimen represented by Fig. 20 seems to indicate that the epithelium of the vermiform appendix, a part of the large intestine, can, as a result of active proliferation of its cells, approach in structure to the type of the glands of the pylorus or duodenum. On another occasion I have seen a single gland of identical structure in an ulcer of the lower part of the ileum.

In discussing these instances of heterotopic epithelium in inflammatory proliferations I have taken a metaplasia or metamorphosis of one kind of cell into another for granted. It now becomes necessary to investigate the manner in which

such a change can be explained, and to inquire into possible alternative explanations of its production.

Differentiated epithelial cells are characterised by the presence of metaplastic granules, fibrils, etc., which are specific for different kinds of epithelium. There is absolutely no evidence to show that a cell can ever cast them off or absorb them and subsequently produce a different set. It follows, therefore, that the metaplasia of an epithelium can never be *direct*, the result of such an exchange of specific characters. Metaplasia is always *indirect*, and produced by long-continued and rapid cell division. Except in tumours, metaplasias are only found in and after subacute and chronic inflammations.

Schaper and Cohen<sup>42</sup> have shown that differentiation and the ability to proliferate are incompatible. The higher the degree of specialisation attained by a cell, the more completely does it lose all power of division. The physiological wear and tear of an epithelium, as well as accidental losses that it may have suffered, are always replaced and regenerated by less highly differentiated basal or germinal cells. But the latter, in normal circumstances, differentiate only into the one kind of tissue, and never into any other kind.

The embryological evidence points to the same conclusion. Schridde's<sup>44</sup> work on the development of the mucous membrane of the œsophagus has been referred to in section II of this paper.

There are three possible explanations to account for the occurrence of heterotopic epithelium as a result of proliferation. They are—

(1) The presence of a group of cells destined originally to participate in the formation of another tissue. They were displaced during development and have remained dormant, to be stimulated to growth and differentiation by the inflammatory process.

(2) Late differentiation of certain cells of the tissue itself, in which its permanent characters have never been unfolded on account of a developmental anomaly. As a result of stimulation by pathological conditions they undergo a belated heterotopic differentiation.

(3) The potentialities that were present during earlier stages of development are re-awakened or re-acquired by the germinal cells of the part (in the sense of Schaper and Cohen<sup>42</sup>) coincidentally with rapid division and proliferation. The pathological stimuli to which they are subjected develop the recessive character in some or in all of them, and a true metaplasia takes place.

Before I discuss these possibilities I must compare the meta-

plasias I have enumerated with the corresponding heteroplasias that arise during development. They agree in that the heterotopic tissue that is produced is always the one that is alternative or recessive at the moment at which the cells acquire their permanent tissue characters. Thus the ectodermal respiratory ciliated epithelium of the nose is converted into the squamous epithelium that is found in its vestibular part, the mesodermal columnar epithelium of the cervical canal into that of the vagina, the cells of the ducts of the salivary glands into those of the buccal epithelium, and so on. In the intestines the appearances are analogous to those described in the heteroplasias and in the remnants of the vitelline duct. Even the squamous epithelium in the epididymis and the vas deferens corresponds to changes found in the remains of the Wolffian body and duct in the female.

This close correspondence of structure warrants the conclusion that the ætiology of the heteroplasias of development and of the metaplasias acquired during adult life is essentially the same.

We will turn now to the first possible explanation of the production of the phenomena under consideration, to the presence of epithelial cells belonging to another organ, and their belated differentiation.

It is very doubtful if cells are ever carried away and displaced by the active growth of an organ. Meyer<sup>32</sup> has insisted that this is a mechanical impossibility in almost every case. A structure like the Wolffian duct grows by division of its apical cell, in very much the same manner as the growing tip of the epithelium on the raw surface of the granulations in Fig. 20. It has to make its way beneath the ectoderm and between the cells of the mesenchyme, and in so doing always follows the path of least resistance. It is quite impossible for it to carry away with it cells of the ectoderm or mesenchyme, even should it have become adherent to them. The only way in which cells that have become separated from, or are abnormally loosely attached to an organ, are displaced to a distance is a purely passive process. Without attempting to enter into this question, I need but instance displacements of suprarenal cortex by the descent of the gonad. They can be found at every point of the path this organ has taken. Passive separation can also take place by ingrowth of mesenchyme in capsule formation, etc.

In order to justify the theory that a heterotopic tissue has been displaced, it must be proved in every case that its cells did actually, at some period of development, come into contact with those of the part in which it is found.

It is a suggestive fact that heterotopic epithelium is most frequently found in the ducts of compound glands (*e. g.* the parotid and submaxillary), and that it has apparently never been seen in a highly differentiated secreting tissue except in the thyroid described above. If its presence were due to displaced cells, there is no reason why these should not be found in every part of the gland. Its preference for the ducts, whose cells are much less highly differentiated than those of the secreting acini, suggests that it has been formed by a metamorphosis of the tissues of the organ themselves.

In parts of the body near the line of union of two distinct epithelia (*e. g.* the nose, cervix uteri, etc.), the difficulties against assuming a displacement of cells are, of course, much less than in internal organs like the gall-bladder, which is as remote from a surface covered by squamous epithelium as it is possible to be. During no stage of development does it come into contact with squamous epithelium, and it never gets a chance to tear away some of its cells, even if it had the power to do so. Squamous epithelium has never been found in a normal gall-bladder in which signs of inflammation were absent and it could be accounted for as a heteroplasia produced at the time of differentiation of the cells of its mucous membrane. But it has been found by Herxheimer<sup>18</sup> in the ducts of the normal pancreas, an organ whose developmental history is very similar. In these and other internal organs a displacement of cells is impossible, and we are driven to one of the alternative explanations of the presence of heterotopic epithelium.

Islands of squamous epithelium have been shown by Meyer<sup>31</sup> to persist under the columnar mucous membrane of the cervix uteri and to play an important part in the healing of the so-called erosions of this organ. But Fig. 16 shows that the presence of this tissue in the polypus of which it is a drawing cannot be accounted for in this manner. A zone of indifferent cells is clearly present here. It undergoes differentiation into squamous epithelium on the surface of the polypus, and into columnar cervical cells in the narrow spaces between the granulations. Whether these indifferent cells be derived from the cervical epithelium or from persistent squamous islands is really immaterial to my argument, since the fact remains that they undergo differentiation in two directions. They possess the prospective potentialities of the mesoblastic epithelium at the moment of formation of the permanent tissue characters of the part.

The question arises: Is it possible for cells, be they displaced or not, to remain in an undifferentiated and therefore

a functionless state for many years, to be more or less accidentally roused to activity by some pathological stimulus? This hypothesis, for it is nothing more, is constantly used with the greatest readiness to explain tumour formation and some other pathological conditions. But when we come to examine the evidence, we find that it points the other way.

I have collected for years all the tissue malformations, including accessory organs and displaced tissues, that I have been able to find. Blastomatous new growths that contain more than one kind of tissue as essential constituents of their parenchyma prove nothing, since they are fully formed tumours, and allow of nothing better than speculations as to the nature of the cells from which they originated. If they are put aside, it is found that all the other displaced and abnormally blended tissues are well differentiated. Only when they are actively growing do their cells present a somewhat undifferentiated appearance. This is, however, no greater than in rapidly proliferating tissues in general.

The evidence therefore shows that displaced cells undergo their normal differentiation and that they do not remain in a dormant state. Lubarsch<sup>24</sup> and Meyer,<sup>34</sup> who have collected long series of tissue malformations, have reached the same conclusions.

The same evidence applies to the second of the explanations suggested above, namely, the delayed heterotopic differentiation of cells of the organ itself, whose permanent tissue characters had not been acquired, and that have therefore remained in an undifferentiated condition. A few pathologists, who have diligently searched for them in organs lined by squamous epithelium, where they can be distinguished by the absence of fibrillation, have found them only in young children. Thus Schridde<sup>45</sup> states that he has been able to demonstrate them in the lips of eight and nine months' fetuses. They are, however, so rare, that he is unable to attach any importance to them. The same writer<sup>44</sup> found a non-fibrillated cell in the basal layer of the mucous membrane of the œsophagus, at a period when the latter had acquired its fibrillation. Herxheimer<sup>17</sup> has drawn attention to the frequent occurrence of small undeveloped glomeruli in the kidneys of infants during the first year of life. They become less numerous with advancing age, and soon disappear, their place being taken by small masses of hyaline tissue. The evidence that cells are delayed in their development is thus very meagre; it is, from its very nature, extremely difficult to collect. But such as it is, it tends to strengthen the argument that these cells do not persist in this

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condition, since they disappear during the first months of life, and either have accomplished their differentiation or else have been destroyed.

The evidence therefore shows that, whereas differentiated cells and tissues can remain isolated for considerable periods of time, it has yet to be proved that undifferentiated cells can do so. For the permanent teeth, for instance, are highly developed organs long before they are erupted. Even dental cysts, branchial and thyroglossal cysts, and analogous remnants are always lined by well-differentiated epithelium. I can see no reason to doubt that the reproductive cells, during their earlier stages, behave in a similar manner. Child<sup>8</sup> has produced much evidence to show that the mature ova and spermatozoa are old, highly specialised and differentiated cells. Their maturation is exceedingly slow, but there can be no doubt that they exert a great and enormously important influence on sexual development throughout the whole period of childhood. They cannot be said to be devoid of functions at this age.

The only cells of the body that normally attain but a slight degree of differentiation throughout the life of the individual are the fibroblasts of the connective tissue. This absence of differentiation is physiological and depends on the fact that it is one of their principal functions to react at once to every kind of injury and to repair as soon as possible every loss of substance that takes place. These offices can be most effectively performed by cells that need not, so to speak, waste time in adapting themselves to altered conditions by the dedifferentiation of a more or less long-continued series of divisions. This is why the degree of differentiation of fibroblasts is slight, enabling them to respond to alterations of environment at once by the formation of the kind of connective tissue matrix which is most suitable in every case.

The epithelia, on the other hand, serve to protect the subjacent tissues and to produce specific secretions. They are therefore modified to such an extent that their power of division is completely lost. The well-known fact has been alluded to above of the presence of less specialised germinal cells which replace the losses incidental to wear and tear and to pathological injury. It is these cells, which alone have retained the capacity to divide, and to give rise to new fully differentiated descendants, that occasionally, after long-continued division, can alone acquire the structure which becomes recessive during the normal development of the part, thereby giving rise to heterotopic or metaplastic forms of epithelium. This is the third of the possible explanations of the nature of the changes involved.

We have seen that the evidence is insufficient to support the others, and this is the only one that remains.

I conclude, therefore, that the metaplasias of epithelium are caused by changes that are set up in the normal cells of the part themselves, cells which in natural conditions would have produced nothing but normal structures. If this be the truth, then a metaplasia is nothing more than a form of regeneration.

It is superfluous to dwell on the enormous differences that obtain between the lower and the higher animals in the extent to which regeneration can take place. With advancing specialisation the structure of the tissues becomes more and more rigid until, as Child <sup>8</sup> (p. 267) expresses it, "in the adult vertebrates the capacity for regeneration is in most cases so narrowly limited that the cells of one tissue are under any known conditions incapable of giving rise to other tissues." One of the reasons why regeneration is usually so imperfect in man lies in the fact that it is the fibroblasts that respond to injury much more rapidly and thoroughly than the other tissues are able to do. They overgrow them and, by their physiological contraction during their differentiation into fibrous tissue, impede their blood-supply and strangle them. But many kinds of epithelium possess a great power of regeneration. The large nodules which are commonly seen in certain forms of cirrhosis of the liver consist entirely of newly-formed hepatic cells. That they cannot compensate for the old liver cells that have been lost, depends on the alteration of the architecture of the organ by the great overgrowth of young fibrous tissue which surrounds the nodules, and on the inability of the young epithelial cells to establish normal connections with the blood-vessels and efferent bile channels.

The fact remains that some of the specialised tissues even in man can undergo a large amount of regenerative hyperplasia. The aim and object of the great majority of regenerations is the replacement of tissue that has been lost. The regenerating cells therefore give rise to descendants of the same kind only.

The case is different when the conditions are altered and it becomes advantageous to the body that cells of another kind be produced. I have stated that, apart from new growths, metaplasias are found only in subacute and chronic inflammations. The conditions that appear to be responsible for their occurrence are all of the nature of irritants. Thus, the respiratory mucous membrane of the nose is readily replaced by squamous epithelium in polypi that are subjected to the drying influence of the air. The same change is found with equal

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frequency in the cervix and body of the uterus when these organs are inverted and prolapsed. Cervical polypi are the result of chronic inflammations, by the irritating discharges of which their surface is constantly bathed. We have seen that they acquire a covering of tough resistant squamous epithelium, which is the form best adapted to withstand irritating external stimuli. The whole series of changes involved has a distinctly purposive character.

So intimately do cause and effect appear to correspond in these cases, that I believe that the one is actually responsible for the other. It is quite unnecessary to invoke developmental anomalies in order to explain the changes, unless we are prepared to admit that they are of almost universal occurrence, an assumption totally opposed to all the available evidence.

Objections have been raised to the possibility of the occurrence of a true metaplasia on the ground that it has never been observed in normal tissues. But we clearly have no right whatever to expect to find it in them, since they are subjected to normal stimuli. We have seen that during development the structure of a tissue depends on its stimulation. If this be normal, the kind of cell that results will be so too. It is only when the stimuli become abnormal that a heteroplasia can be produced. The difference between it and a metaplasia depends on the fact that the former is a differentiation of incompletely specialised cells, whereas the latter depends on the reappearance of heterotopic characters in a tissue which has already acquired its permanent characters.

This difference raises the question : Is metaplasia the result of a dedifferentiation of the germinal cells of the epithelium, or is it developed simply in response to altered conditions? That it is not, in the true sense of the word, the reacquisition of a character that has been lost is, I think, obvious. Metaplasia is, as we have seen, induced more readily in some parts of the body than in others, its frequency varies with the degree of differentiation of the cells, and it is always associated with long-continued proliferation. All these facts point to dedifferentiation. So does the fact that, as has been shown by Schridde,<sup>44</sup> the basal cells of a squamous epithelium are fibrillated, whereas columnar cells are not. On the other hand, the same observer has shown that the goblet cells found in ectopia vesicæ retain traces of fibrillation. The truth appears to be that the potentiality for metaplasia is an inherent character of certain kinds of epithelium, but that it requires a varying amount of proliferation and dedifferentiation for its development in different parts of the body.



I cannot enter into the question of the occurrence of dedifferentiation in general in the higher animals and in man. It is one for biologists to settle, and has been very ably advocated by Child in his most suggestive *Senescence and Rejuvenescence*.

The heteroplasias of development and the metaplasias resulting from the accidents that affect the finished adult tissues agree in that they depend on abnormal stimulation, which brings out and makes apparent the alternative recessive characters of the part.

*Conclusions.*—(1) The recessive tissue character reappears occasionally at every time of life as a result of chronic inflammation. To this phenomenon the name of "metaplasia" has been applied.

(2) The ease and frequency with which this change can occur varies within wide limits in different situations. They are greatest near external orifices and in ducts, and very rare in secreting glandular epithelium. This depends, in great part, on the degree of differentiation the cells have undergone.

(3) This change in the character of the epithelium is always associated with a marked amount of proliferation of its cells, and is to be regarded as a form of regeneration.

(4) When suitable material is examined, undifferentiated cells are found that clearly undergo differentiation in two directions. They thereby give rise to cells that are of the type that is dominant, as well as to others that are recessive for the part.

(5) The evidence goes to prove that these changes take place in the normal germinal cells of the part.

(6) A metaplasia is induced by the action of abnormal stimuli on actively proliferating cells. They are the drying influence of exposure to air, the macerating action of irritating discharges, and other conditions of a similar, but often obscure, nature.

(7) These conditions are most frequently to be found near external orifices. The relative frequency of metaplasia in these situations is accounted for much better by their action than by the assumption of a special predisposition of the cells of these parts.

(8) The occurrence of metaplasias shows that, at the period of development at which the dominant permanent tissue character is acquired, the alternative recessive character is only suppressed and not utterly lost.

## SUMMARY

I have collected these anomalies, most of which are well known to pathologists, since they are characterised by the fact that they are essentially anomalies of position. They are built up of normal cells, combined and arranged in an orderly manner to form tissues and organs, many of which attain to a high degree of perfection of structure. I have named them heteromorphoses, a designation that has often been applied to them before.

They can be subdivided according to the time of life of the individual at which they have taken place, and to the amount and degree of the changes in the cells that have led to their formation. The classification I have adopted is based on the period of their inception; some, such as the epithelial heteroplasias, have been produced during development, others at a later period of life.

They can all be referred to anomalies of differentiation. These may be abnormal merely in extent; in excess of the degree of differentiation characteristic of the tissue. Examples are the prosoplasias of epithelium, and the differentiation of embryonic tissues whose usual fate it is to be absorbed. Again, they may be abnormal in the direction differentiation has taken; a tissue results which is not usually found in the part of the body implicated.

Their chief interest depends on the light they shed on growth and development. They suggest that differentiation is, within wide limits at all events, the result of stimulation from without, of environment in fact. When this is normal, differentiation will inevitably be so too; when cells are exposed to abnormal influences they will as inevitably undergo differentiation in an abnormal direction.

In all the instances that have been considered it is unnecessary, if not wrong, to assume an inherent vicious predisposition of the cells, until all the numerous possibilities of the influence of environment have been exhausted. We are only beginning to appreciate how great these are from the work of the experimental embryologists.

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## ASTLEY COOPER

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### PART II

#### LIGATURE OF THE CAROTID ARTERY

HUNTER ligatured the carotid artery of a young deer in Richmond Park by permission of the King. He observed that the half-grown antler became cold and that growth was arrested. In a few weeks he found that the antler had again become warm and was growing. On dissecting the parts later on he discovered that the return of the blood supply, and consequently the growth, was due to enlargement of the anastomosing vessels above and below the ligature.

The application to aneurysm at once suggested itself. His confidence in his conclusions was shown, when in 1785 he ligatured the femoral artery for popliteal aneurysm with success. Up to this time the opening up of the sac and the ligature of the vessel above and below had been attended with so great a mortality that many surgeons advocated immediate amputation. Thus was established the principle of ligature some distance above the sac. Hunter a year later, in making a comment on this epoch-making operation, says that "in future I would use only one ligature."

At this date Astley Cooper was in his first year, and very soon must have heard of the operation from Cline. It was for others to extend the application of the principle established by Hunter, and with this object Astley Cooper made numerous experiments on all trunk vessels, especially on the carotid arteries. He ligatured these vessels singly, and later in succession at intervals, and then both simultaneously in dogs, without ill effects. Then followed ligature of the vertebrals alone or in association with the carotids. Lastly he ligatured both carotids and both vertebrals, accomplishing this feat in half an hour, surely a tribute to his technical skill. One dog survived, and later, being killed and injected, the anastomatic circulation was displayed.

The object of this investigation was to determine which

arteries were most essential for the nourishment of the brain, as well as to inquire whether there was any ground for the objection that enlargement of the vessel would be interfered with by the bony canals through which they passed. To make the investigation complete he ligatured the vagus and sympathetic nerves. The account he gives of this investigation in the first volume of the *Guy's Hospital Reports* shows his method of research, his industry, and his determination to arrive at the truth.

It was these experiments that brought into prominence the fact of anastomatic circulation.

Now came the opportunity to put into practice on the human subject the ligature of the carotid. Astley Cooper was well aware of the general view that the brain would suffer and that many would condemn the attempt. One gathers this also from Travers' defence of the operation when recording his own case, the second to be performed. But with a confidence based, as will be shown later, on the findings of morbid anatomy and on experiment, he was not deterred, and was prepared to encounter any criticism. The first operation took place on November 1, 1805, the patient being a woman, aged forty-four, with an aneurysm of the right carotid. The report was read at the first meeting of the newly constituted Medico-Chirurgical Society on January 29, 1806.

It was a difficult case, for the aneurysm occupied two-thirds of the neck, and the skin over the most prominent part was thin, and great doubts were expressed as to whether there was room between the clavicle and the sac for the application of a ligature. The patient sat up in a chair, and in the presence of eight surgeons and visitors two ligatures were applied about half an inch apart, being the greatest distance which they could be separated. "I thought it proper," he writes, "not to run the risk of hæmorrhage by dividing the artery, as I was fearful the ligatures would be thrown off by the force of the heart." There was no immediate hemiplegia, and thus the information gained from observation and experiment was confirmed. On the eighth day, however, after a violent fit of coughing left hemiplegia occurred. From what we have learned of late, this was probably due to the separation of part of the clot.

The ligatures came away on the twelfth day, but the woman died on the twentieth day from suppuration of the sac, with pressure on the larynx and pharynx. The carotid was found closed "by the adhesive process, and by a clot which adhered strongly to its coats." The neighbouring structures had not suffered any injury. Permission to examine the brain could

not be obtained. He was not deterred by this want of success, for he had established two facts : first that " the carotid may be as safely tied as any other artery in the body," and secondly that cerebral injury will not of necessity ensue. He writes that the failure was due " to the operation being too long deferred, and that it will not prevent my performing it in any case in which the disease is somewhat less advanced." One can well imagine the remarks that would be made by his critics.

A second opportunity came on June 22, 1808, the patient being a man of fifty with a small aneurysm, probably of the internal carotid. After securing the ligatures, one end of each was carried through the artery, the one below and the other above the site of the ligatures, and again tied. The vessel was then divided. The operation was performed in the presence of several surgeons and visitors, among whom was the Parisian surgeon, Dubois. The case was described before the Medico-Chirurgical Society on February 21, 1809, by which date the tumour had disappeared.

In commenting on this case he says he " had no apprehensions of the functions of the brain sustaining permanent injury from a ligature of the carotid artery, for I had the evidence of Dr. Baillie to prove that one carotid might be entirely obstructed, and the diameter of the other considerably lessened in the same person, without any apparent ill effects. I have also given a drawing in my former paper of the left carotid being obstructed by the pressure of an aneurysm of the aorta," and he then refers to his experiments on dogs " many years ago," which I have already referred to.

This second patient died in 1821, thirteen years later, from apoplexy, and Astley Cooper, taking Key and his assistants, went after his evening lecture to make the autopsy. The arteries were injected through the aorta, and the preparation of the brain is figured in the first volume of the *Guy's Hospital Reports*. The common carotid was found obliterated in its whole extent. To indicate the views held by most surgeons of the day, and to emphasise the progressive character of Astley Cooper, I may quote a remark by Travers, who had successfully ligatured the common carotid on May 23, 1809. In reporting the case (*Med. Chir. Trans.*, II, November 1, 1809) he says, " It is worthy of detail on two accounts, first because it furnishes a second conclusive example of the safety of an operation, which has been commonly regarded impracticable or injurious to the functions of the sensorium ; and secondly because it determines the influence which by the ligature of the carotid trunk we possess over the diseased condition of its branches."

## LIGATURE OF THE EXTERNAL ILIAC ARTERY

This operation was performed on June 22, 1808, the same day as the second case of ligature of the carotid. Abernethy had previously ligatured this vessel in 1796. The skin over the aneurysm was tense, purple, and thin. The method of securing the ligature was the same as that adopted in the second carotid case, and the artery was divided. The man died in 1826, eighteen years later, and at considerable expense and trouble—for he lived in the country—the specimen was obtained and injected. A full description is given in the first volume of these *Reports* with coloured illustrations, and the dried preparation is preserved in our Museum, and shows very beautifully the anastomotic circulation. In the same year Aston Key tied the external iliac, approaching the vessel by the method of Cooper, but using a single ligature. The man was stout and the resistance of the muscles added to the difficulties.

## LIGATURE OF THE AORTA

Finally comes the culmination of his experiment on the ligation of vessels—the ligation of the aorta. In the paper read before the Medico-Chirurgical Society in June 1811, referring to the observations and experiments leading up to the ligature of the carotid, he says, “Lastly, I was anxious to ascertain when even the aorta was tied if the blood would still find its course by anastomosis.” This he had demonstrated two years before in dogs. “During last winter, assisted by Mr. White and Mr. Dean, two of our most promising pupils, I repeated the experiments and have the honour of showing to the Society the aorta tied and divided, the animal having survived the experiment and maintained his usual health!” In Volume II of the *Transactions* there is a coloured illustration of the injected specimen. A specimen of successful ligature of the aorta in a dog will be found in the Museum at Guy’s Hospital. He had thus prepared himself for such an operation on man should the occasion arise, and it came six years later. In bringing the case before the Society he was well aware that criticism would arise just as it did in the case of the carotid.

“I fear that the title of this paper may impress the reader with an idea that nothing could justify me in performing the operation which I am about to describe, for that a ligature made upon the aorta must necessarily prove fatal, but I trust that it will be seen in this sequel that the operation was not attended with the immediate danger which might have been apprehended; that the patient complained of but little pain during the *per-*



*formance*, that it afforded the only hope of safety, and that we had to lament not that the operation was performed, but that it had not been sooner done. Sorry indeed should I be to sport with the life of a fellow-creature who might repose a confidence either in my surgical knowledge or my humanity."

The case was that of a man of thirty-eight, admitted May 9, 1817, with an iliac aneurysm, extending from 3 to 4 inches above Poupart's ligament to an equal distance below, and was of great magnitude. A sudden enlargement occurred three days later, doubling the size, and a further increase occurred on the 16th. On the 20th and 22nd the skin gave way and hæmorrhage occurred. On the 25th profuse bleeding took place, but happily Aston Key was near and was able to control it, but the exhaustion was severe. At 9 p.m. Astley Cooper was summoned, and thinking it might be possible to secure the artery through the sac, he made a small opening and introduced his finger, only to find that "the vessel entered the sac above and quitted it below without there being any intervening portion of vessel." Was the man to be left to his fate? It was clearly in Astley Cooper's mind that he might be called upon to ligature the aorta, and this not by the lateral incision, rendered impossible owing to the position of the aneurysm, but by some other route. Two days before he had inquired whether there were any bodies in the post-mortem room, and finding two, he proceeded to tie the aorta through the peritoneum, using a small opening. The "pupil," who records this observation, says that it was found difficult, and evidently Cooper was not over-satisfied. I mention this to emphasise the dexterity he displayed in the actual operation. The scene, as described by Astley Cooper himself, is dramatic.

"As I was quitting the patient's bedside I felt great regret in which all the students by whom I was surrounded joined me, that the patient should be left to perish without giving him the only chance which remained of preventing his immediate dissolution from hæmorrhage by tying the aorta, and therefore said, 'Gentlemen, this only hope of safety I am determined to give him.'" He therefore in his usual kindly way explained the position to the patient, who replied, "Sir, I leave myself in your hands."

"A three-inch incision skirting the umbilicus was made through the linea alba; with the finger the peritoneum was scratched through on the left of the aorta, and worked under the vessel to the right and again through the peritoneum. The needle carrying the long silk ligature followed, Aston Key securing the silk as the needle was withdrawn. To be sure of excluding the bowel, the ligature before being tied was held

taut, while the finger was passed down between the threads. The omentum was drawn behind the ligature to facilitate adhesion, and the knot was left out of the wound." One can appreciate the surgeon's gratification on going to the bedside at one o'clock next day, to find the man adjusting the bed-clothes, free from pain and cheerful. Vomiting, however, ensued almost at once, and it would appear from the clinical notes that the patient died of peritonitis, though at the inspection made in the presence of Cooper, Travers, and others, "not the least appearance of peritoneal inflammation existed." Astley Cooper knew well what these appearances were, for he often mentions them in hernia. The man lived forty hours, the right limb recovered its warmth and sensation, but the left was livid and cold, which Cooper attributed to the pressure of the aneurysm. The ligature had closed the aorta without injury to any neighbouring structure. Accuracy could not have been greater. There was a clot of one inch above the ligature, another of an inch in the right common iliac, and of three-quarters of an inch in the left. It was unfortunate that, as in the carotid, so advanced a case should have presented itself for a first attempt, though it serves to display the courage of the surgeon and his indifference to criticism, when convinced of the truth of his conclusions.

In this paper he discusses the question of ligature generally, refers to the suggestion of Lawrence that fine silk should be used and cut short, and to the introduction of catgut, and records the successful employment of this material on the popliteal artery in a man of eighty. It was prepared by soaking in water at 100° F. The ends of the ligature were cut short, and primary union resulted. He gives his reasons for using this material, and in his cautious way says, "I shall give the result of the trial I have made, wishing to be understood that I consider the subject at present as undecided, and only as one for future investigation." Commenting on the recovery he says, "The case gave me much pleasure, and the rapid recovery leads me to hope that the operation for aneurysm may become, at some future period, infinitely more simple than it has been rendered to the present moment." It is impossible not to stand for a moment in admiration of the man who could conceive and carry out ligature of the aorta, and thus arrest the circulation in the lower half of the body. Astley Cooper had by pathological observation and by experiment convinced himself that it was possible; there lacked but one fact, that of an instance of obstruction of the abdominal aorta from disease. He recognised that approach from behind the peritoneum was in this case impossible, and well knew the added risk of the trans-peritoneal route. The dexterity and

the accuracy secured could not have been equalled by any other surgeon of the time, for no one seems to have pursued the experimental method to such an extent. Moreover, he had, as he says, contemplated the possibility, and no doubt had intended to proceed by the post-peritoneal route. It was a bold decision to run the risk of peritonitis in those days.

By the failure he was undismayed. The circulation in one limb had so far recovered as to justify the conclusion that, given a less extensive disease and a better general condition, recovery would have followed.

Dexterity and rapidity counted for much in those days, and both these Astley Cooper possessed in a degree unequalled by anyone, qualities the outcome of his many operations upon animals and his knowledge of anatomy.

The operation seems to have been repeated by two others in Astley Cooper's time, by James of Exeter in 1829, and by Murray in 1834, who took the post-peritoneal route. Both were unsuccessful. The survival of one case for ten days in 1842, death being due to secondary hæmorrhage, justified Cooper's confidence as to the circulation.

#### PUBLICATIONS

Astley Cooper was, like Hunter, in no hurry to publish his work. He made it a rule never to make any statement he had not verified by his own observation, and to accomplish this much time was required, besides an immense amount of original investigation. His first and greatest work is that on *Hernia* in two large quarto volumes. The first part was issued in 1804 and was dedicated to his "Master in Surgery, Mr. Cline," to whose influence he pays a warm tribute. The second part was dedicated in 1807 to Monro of Edinburgh. In order to keep down the price, Cooper bore the whole cost, losing a thousand pounds over the transaction. I have referred in the first part of this essay to Cooper's visit to the northern capital and to his relations with the great anatomist. I shall later on give some extracts from this work and will only repeat that no one should fail to make acquaintance with these volumes. The *Treatise on Dislocations and Fractures* appeared in 1822 and went through several editions; the sixth was published in 1829 and was translated into several Continental languages. Then followed the *Treatise on Diseases of the Breast* in 1829, dedicated to Mr. Harrison, the treasurer of Guy's Hospital, and in the following year that on the *Testis*. Two years later appeared the *Anatomy of the Thymus Gland*, and finally, in

1840, at the age of seventy-two, his work on the *Anatomy of the Breast* was issued. In the following year he died. This volume is dedicated to the Members of the Medical Profession, whom he addresses as "My dear Brethren." He expresses his delight in observing their increased love for the science of the profession, and then thanks them for their unwearied kindness and attention during a period of fifty years. "If," he concludes, "this work adds anything to your knowledge of the anatomy of the breast, I shall have received the utmost and only reward which I am anxious to obtain by its publication." It was the swan song of a great teacher!

Besides these large works, he published many papers in the *Guy's Reports* and in the *Transactions of the Medico-Chirurgical Society*. His surgical lectures were first published in the *Lancet* in 1823-1824, and as this was the first time such a record had been published by a medical journal, much comment was aroused. Cooper was charged with advertising himself.

Later the lectures were issued in a small volume, which was no doubt the text-book of the day and was widely read at home and in America, where many of his pupils were in practice. There are in the library of the College of Surgeons several manuscript copies of the lectures, and of those that have been printed the best is that by his old apprentice Tyrrell, who became surgeon to St. Thomas's Hospital. Tyrrell's edition of Cooper's lectures will well bear perusal, for therein will be found many observations and methods which, forgotten for years, have been in later times considered as novel.\* Let us take, for instance, his method of amputation at the hip joint. "It is," he says, "decidedly the best plan to secure the femoral artery at Poupert's ligament as the first step in the operation"; and again he says, "I am of opinion that in every case in which the amputation can be performed by sawing through the bone below the attachment of the capsular ligament, that it should be done in preference to opening the joint." The first of these methods has of late years become the established practice, while the wisdom of the second has been amply confirmed.

One of the most valuable lectures is that on the treatment of compound fractures of the ankle joint, in which he advocates the preservation of the limb. He describes fully the removal of every particle of dirt, of all loose pieces of bone, enlarging the wound when necessary, and occasionally removing a portion

\* The edition is in three volumes, the first published in 1824, the second in the following year, and the third in 1827. The chapter on hernia might, with one omission—the use of the tobacco clyster—be set in a modern text-book.

of the tibia or astragalus. A case is related as occurring in 1797, in which, besides the dislocation, the astragalus was broken into many pieces, several of which, being detached, were removed. The wound was covered with lint, soaked in the patient's blood. In nine months he returned to his employment.

Amputation was, I believe, the common practice for such injuries up to 1880, except in the hands of the few who followed Lister, so that we had retrograded from Sir Astley's time. I well remember my own satisfaction at the rapid recovery after such an injury in 1883, and it was then considered something of a novelty.

#### STRANGULATED HERNIA

From the lecture on strangulated hernia a few extracts will show how far he had advanced. To obtain a more complete knowledge the original publication should be consulted, not only on account of the sound practice advised, but also for the life-sized illustrations of the anatomy of the parts concerned and of the morbid conditions. When one recalls the practice in 1874, when the writer first entered the wards, taxis being the routine, it is with no little astonishment that one reads the following: "Very frequently much time is lost before an operation is performed; and too much cannot be said in condemnation of such practice. The patient is submitted again and again to the taxis, and the swelling is rendered extremely tender by being so often compressed in the hope of avoiding an operation, until at length the rapid increase of the symptoms point out the impropriety of such delay, and an operation is performed when but little prospect of success remains."

Again he writes: "The cause of a person dying after operation is not to be attributed to the operation, but to the degree of mischief which has taken place previously to its being performed." And yet fifty years and longer after this was written the operation was considered so dangerous that medical men delayed sending up the cases, the patients refused operation, and the senior surgeons of 1870 to 1880 often acquiesced in a delay which proved fatal. Even in 1882, when the writer was first called to operate for strangulated hernia, and convinced of the safety of the antiseptic methods, he was one of ten who failed to persuade a patient to submit to operation, and in private the struggle was sometimes equally great.

In referring to four fatal cases of femoral hernia, he writes: "These four cases point out the danger of delay, and so strongly

am I impressed with this belief, that if I myself were the subject of strangulated hernia, I should only try the effect of the tobacco clysters, and if they did not succeed, would have the operation performed in twelve hours from the assession of symptoms.

“My mode of avoiding injury to the epigastric or obturator arteries, is to make a very slight division of the stricture with the knife; and then by pressure of the finger or of a director, to enlarge the opening.”

This is a sound practice and will, as he says, always avoid injury to the artery. The too free use of the hernia knife has been responsible for the accident. To avoid this a flat director carrying a sharp ridge was at one time in use, but Cooper's method is superior. Indeed less is sufficient. The writer, called to a strangulated femoral hernia in private, was aghast to discover that he had omitted to take his hernia knife. Not allowing this to be suspected as an omission, he used the blade of a pair of detachable scissors, and with such success that the hernia knife was in future abandoned as an unnecessary instrument. After nicking the stricture the gap was stretched by a director. Had Astley Cooper's practice been known, probably the knife would never have been used.

Cooper always opened the sac, and directs that the opening be made at the lower part, because the bowel does not often reach so far. He held that the constricting cause was outside the sac at the external or internal ring. Yet he says that if division external to the sac does not succeed, the knife must be passed inside. “As to what has been said by surgeons of stricture being formed by a thickening of the orifice of the sac,” he writes, “I shall have occasion to show that the stricture is not in the sac, as has been supposed, but in another part external to it; at the same time, however, I would not be understood to deny altogether this alteration in the mouth of the sac, nor to state my belief founded on dissection that it is a rare occurrence.”

On the question of the management of gangrenous bowel, and especially of resection and suture, he writes very fully, and describes a series of experiments carried out on dogs. He mentions the danger of placing sutures in the injured bowel, and advocates a free removal to reach healthy tissue. Three sutures of silk were used, the ends being left out of the abdomen, and he particularly states that one should be at the mesenteric border.

In one successful resection on a dog “a cylinder of isinglass was introduced into the bowel and three sutures were made upon it. In three days the animal had regular stools. On

the sixteenth day he was killed and the united portion of the intestine shown to the students." In the next experiment he omitted the isinglass cylinder because it was compressed by the bowel. This would appear to be the earliest employment of a bobbin, which was in vogue for a brief period some fifteen years ago.

Then he discusses the merits of longitudinal and transverse suture, and to produce a condition more resembling strangulated intestine he allowed a loop of bowel to protrude from an abdominal incision for some time before operating.

#### COMPARATIVE ANATOMY

In June 1813 Astley Cooper was called upon to deliver the course of lectures in Comparative Anatomy, established at the College of Surgeons under the agreement with the Government when Hunter's Museum was handed over to the College. He would have preferred the associated lectureship on Surgery, but this was allotted to Abernethy. He undertook the task with some reluctance, partly because he was already fully occupied, and partly because he did not feel qualified to deal adequately with the subject. He was still lecturing on Anatomy and Surgery at St. Thomas's and Guy's, was surgeon to the hospital with its attendant clinical teaching, and besides was at the height of his practice, for it was in this year that his income reached the unprecedented figure of £21,000.

As to his qualifications, it must be said that comparative anatomy in his scheme of things took a subsidiary place. It is true he dissected over many years the dead animals from the menagerie at the Tower, including the famous elephant, and it was known amongst butchers, fishmongers, and birdsellers that there was a ready market for anything unusual in Jeffries Square. Besides this, Astley Cooper had from his earliest years in London conducted experiments on animals as part of physiological research. He was no doubt prepared to discuss the comparative anatomy and physiology of the thymus or the thyroid glands so far as they were known. It was his practice to devote three or four lectures at the end of the course in anatomy to the structure of the lower animals, and to illustrate these lectures by preparations, many of them beautifully prepared and injected, as may be seen from the examples in our Guy's Museum and at the College of Surgeons. Still, as I have said, the subject had with him a secondary position. The anatomist and physiologist sought amongst the lower animals for light to unravel the more complicated meaning and action

of the human machine, and ever and always it was the surgeon calling to lower life for information, guidance, and help in the greatest work of all, the explanation of life and the alleviation of human suffering. Notwithstanding these misgivings, he felt it a duty to undertake the lectureship. There was no one else the Council could ask, for Blizzard and Horne had already delivered the lectures. Astley Cooper determined to see what industry could do. He had always worked on independent lines, and knew little of the work of others, except that of Hunter and his English colleagues. There were nine months in which to prepare a course of twenty-four lectures, and with characteristic energy he set to work, with the aid of his assistants, to dissect fishes and animals, and perform what experiments were required. He dispatched his nephew and one assistant to Weymouth, having heard that rare and curious fish were brought by the trawlers. Specimens were partially dissected and sent to London in spirit and then prepared. To accomplish this work without diminishing that in which he was already engaged, he rose at 4 a.m. and dissected by candle-light till eight o'clock, when he began his usual day's work, which kept him busy till midnight, for many visits were made after dinner. The lectures in March 1814 were cut short by the death of his adopted daughter. In 1815 he gave fifteen lectures, largely on digestion, and according to Clift the attendance never fell below 300. Clift says specimens came in coach-loads and were well prepared and injected. Astley Cooper, commenting upon the result, remarks that he could have done much better and had larger audiences had the subject been Surgery. He had fulfilled the task, but at a cost, for it was after this great effort that signs of the vascular changes, which ultimately led to his death, first made their appearance. I cannot believe that Astley Cooper undertook these lectures from the notoriety he might gain as Hunterian Professor, but rather out of a sense of duty and a regard for the Council's request.

It was in these lectures that he wrote the names of some of his friends on pieces of bone covered with a material impervious to the gastric juice. These having been swallowed by dogs and withdrawn after an interval, the letters were found sunk in the bone. He reversed the proceeding, when the letters stood out from the surface. The Museum at Guy's contained, when the writer was a student, a large number of Astley Cooper's preparations. There were fine injections of the lymphatics of the testis and epididymis with quicksilver. Very few of these now remain. There are some of the thymus and thyroid, and



the lymphatics of the breast in the Museum of the College of Surgeons, and a few remain at St. Thomas's.

The skeleton of an elephant still occupies a place in the Guy's Museum, attached to which is an interesting history. The creature was one of the attractions at the menagerie in the Tower. On its death the carcase was with no little difficulty conveyed through the front gates in Jeffries Square, but it was found impossible to get it into the outbuilding used as a dissecting room. It was left in a corner of the yard, a piece of carpet being hung over the railings to exclude the gazing crowd, and here the dissection went on. Every organ was examined and the skeleton preserved and articulated. Some of the students assisted him with the heavier parts of the work. The ribs of this elephant seem to have been broken in many places, and united by what looks like external callus only. These fractures presumably were due to the keepers' attentions.

#### THE OPERATION ON KING GEORGE IV.

In undertaking the operation on King George IV., Astley Cooper was placed in an awkward position. It was through the Prime Minister, Lord Liverpool, whom Cooper had attended, that his fame as an operator had become known to the King. Together with Sir Everard Horne and Sir Benjamin Brodie he went to Windsor. The sebaceous cyst on the scalp of the King was then inflamed, and it was deemed wise to delay removal.

In the spring of 1821 Astley Cooper was summoned to Brighton to see His Majesty. About one o'clock in the morning the King came into Cooper's room and asked him to remove the cyst there and then, saying, "I am now ready and wish you to remove this thing from my head." The risks and the importance of his life were pointed out to him, and Cooper urged moreover that before consenting he would like the opinion of Mr. Cline. The King replied, "This is the second time I have been disappointed, and I will have it removed when I come to town." Astley Cooper went to the Prime Minister, and requested him to persuade the King to let Sir E. Horne do the operation, as he was Serjeant Surgeon, from which it will be seen that Cooper was averse from doing it. Horne wrote to Cooper that he proposed operating on the Wednesday, and there gathered in consultation Horne, Halford, Tierney, Cline, Brodie, and Cooper. Cline said, "Who is to do the operation?" Cooper replied, "Sir Everard." Sir Henry Halford was called out of the room, and on returning

said to Astley Cooper, "You are to do the operation." Having come unprepared, he borrowed instruments from Horne. Almost immediately the King entered. The cyst did not turn out as was hoped, for it was adherent to the skin and required a good deal of dissection. Astley Cooper having completed one half, passed the scalpel to Cline, who was assisting. Cline then removed the other half.

On Saturday, while Astley Cooper was at work with one of his assistants, an urgent message arrived to say the King was in great pain. Cooper, turning to his assistant, said he feared erysipelas, as this was just the time for its onset. On his arrival at the palace the King said to him, "I have not slept all night. My head is sore all over." As may be imagined, Cooper had an anxious day, but on calling next morning he found the King with an attack of acute gout in the foot, and after this all went well.

No doubt Astley Cooper felt that a disaster would seriously affect his position, and for this reason was particularly insistent that Cline should be present, for he writes: "Mr. Cline, the world would say, would not advise anything without due consideration, and from my long knowledge of him, I should like him to assist me, and he would not object to bear a part of the onus under any circumstances."

Later on he became Serjeant Surgeon and enjoyed a similar favour under the next Sovereign. The King himself spoke of the honour of a baronetcy, which the Prime Minister proposed to confer on him. Astley Cooper replied that, as he had no son, such a distinction would be of more value if it could pass on his death to his nephew whom he had adopted. "Then let it be made out as you wish," was His Majesty's reply.

The whole story very well illustrates the surgery of the time, with the dangers attending even simple operations, and also Astley Cooper's reluctance to undertake the responsibility. He had had an attack of giddiness in the presence of a distinguished patient, and the fear of a recurrence on such an important occasion added to his anxieties.

#### ASTLEY COOPER AND MEDICAL SOCIETIES

I have referred to the active part Astley Cooper took in the discussions at the Guy's Physical Society, and the educative value he attached to such gatherings. Recognising that the discussions were too advanced for the ordinary pupils, he established a society for the apprentices and pupils of the two hospitals, which existed for several years. One volume

of papers was issued, and in this appears the first publication by Astley Cooper in 1798. He records a case of strangulated diaphragmatic hernia, in which a part of the abdominal viscera was protruded into the cavity of the chest. This condition was found in the body of a female in the dissecting room. With infinite trouble he traced the clinical history, and found that she had been subject to sudden attacks of pain and vomiting, in the last of which she died after four days' illness. After discussing the cause of the aperture in the diaphragm and referring to cases published by Morgagni and others, he concludes that it was a malformation.

The successor to this students' society was the "Clinical Report Society," and it is of interest to note that it was flourishing when Sir Samuel Wilks was a student. In his *Biographical Reminiscences* he thus refers to it: "During my studentship I was a member of the Clinical Report Society. This was a voluntary association of students, who in the third and fourth year of their pupilage joined together for the purpose of more thoroughly studying the cases in the wards, and so elevated themselves above those who were "walking the hospitals" to use the expression of the time. The members of the Society met once a week, and at the end of every half year a report was drawn up by the Secretary, there being one on the medical and another on the surgical side."

The foundation of the Medical Society in 1773 drew off many from the Physical Society. The meetings were held in Bolt Court, Cornhill, at a time when there was a large resident population and in consequence many medical men in the city. Though the Clinical Report Society still survived in 1853, when Sir Samuel Wilks was a member, the Physical Society soon became more a students' society and thus finally took its place.

In 1808 the Medico-Chirurgical Society was founded. Astley Cooper became the first treasurer. To the Transactions he communicated many valuable papers, the first volume containing an account of his ligature of the carotid.

Thus we see that he recognised the value of such personal association and of submitting his opinions to the criticism of others. On the same subject Osler wrote:

"No class of men needs friction so much as physicians; no class gets less. The daily round of a busy practitioner tends to develop an egoism of a most intense kind to which there is no antidote. The few sets-back are forgotten, the mistakes are often buried—ten years of successful work tend to make a man touchy, dogmatic, intolerant of correction, and abominably self-centred. To this mental attitude the Medical Society

is the best corrective, and a man misses a good part of his education who does not get knocked about a bit by his colleagues in discussions and criticisms."

#### ASTLEY COOPER AS AN EXAMINER

In 1822, at the age of forty-four, Astley Cooper was elected to the Court of Examiners at the College of Surgeons, an office which afforded him no little gratification, not only on account of the honour of such a position, but also for the opportunity it afforded him of employing himself to the advantage of the public in testing the efficiency of the candidates.

He considered the honour of the College demanded the most careful discharge of the duties, that it might hold a foremost place amongst our national institutions.

His biographer, who was for some time a co-examiner, relates that he gave much thought to the form the examinations should take, in order to convince himself that the candidate had legitimately acquired his knowledge and not merely crammed. He showed much consideration and kindness of manner, and was scrupulously fair in his questions.

Later, when as President it became his duty to reject candidates, "he found it a painful task, and mingled his disapprobation with friendly advice and encouragement. And not only thus did he endeavour to assuage the disappointment, but he frequently wrote to the parents explaining the circumstances, so as to mitigate their regret, and assure them that a few weeks' further study would no doubt secure the coveted diploma for their son." These letters were written concerning those of whom he knew nothing, as well as the pupils from his own school.

The following comment suggests that he was not over-pleased with some of the older examiners. It must be recollected that there was no time limit as exists now, and that some examiners continued long after they had ceased to learn themselves.

"A man who is a member of that Court (the Council of the College of Surgeons) must continue to study. It is not enough for him to say, 'Now that I am highly qualified in the profession, I have nothing more to learn.' It is his duty to learn every day in his life, and if he does not keep up his knowledge, the boys will consider him, and treat him, as an examiner, with contempt.

"Whenever a man is too old to study, he is too old to be an examiner; and if I laid my head upon my pillow at night,

without having dissected something in the day, I should think that I had lost that day. I do think a man must keep up his knowledge to the last."

#### ACKNOWLEDGMENT OF THE WORK OF OTHERS

Astley Cooper was a man who spoke fearlessly, and no doubt offended not a few of his contemporaries. He was accused by Charles Bell of adopting as his own the observations of others, and this distinguished surgeon devoted a long lecture, given at the Windmill School, to condemn the iniquities of Astley Cooper in this respect. He referred particularly to his observations on fracture of the neck of the femur, claiming these as the original work of his brother John and himself. The truth no doubt is that all three had been working on the same subject and had arrived at very similar conclusions.

Cooper made no reply to this attack, but contented himself with a reference to it in the introduction to one of his publications, in which he disclaims any intention of borrowing the labours of others and rejoices in the rise of the younger men.

He frankly acknowledges that he relied upon his own observations, for the teaching was vague and traditional. He felt that progress could alone be made by individual research, and was prepared, like Hunter, to find himself in opposition to the received opinions.

In the introduction to his work on *Hernia*, he says, "I have almost uniformly in the following work avoided quoting the opinion of authors on this part of surgery. This I have done, not from any wish to undervalue the labours of some of the most excellent physiologists and practitioners that have adorned our profession, but because it did not form part of my plan to give a history of this branch of surgery, and because I wished to confine myself to the very wide scene of observations afforded by the two noble institutions of St. Thomas's and Guy's Hospitals and to that portion of the practice of the metropolis which I have personally been able to authenticate. I have therefore related no case, and given no remark to the truth of which I cannot vouch."

It is with no stint that he acknowledges his debt to Hunter. "He was a man," he writes, "who thought for himself. He was the most industrious man that ever lived. His vast museum is a proof of what industry can accomplish, for it contains matter for seven years' investigation, and it took Clift ten years to catalogue the specimens."

He knew Hunter sufficiently well to assist him in the dissection of a whale, and to talk to him after the lectures.

Cline he almost venerated, and it was a grief to Astley Cooper that an estrangement arose during the later years of his master's life. This was probably due to the part Cooper took in bringing about the independent establishment of the school at Guy's. His reliance upon Cline's judgment I have referred to when writing of the operation on King George IV.

He calls him "My most able and judicious preceptor." In the dedication of the first volume on *Hernia*, he acknowledges "that many of the ideas which it contains have been derived from your public and private instruction," and adds "that you may long continue to enjoy an exalted professional reputation, acquired solely by merit, and unsullied by a single unworthy act, is the ardent wish of, Your sincere friend and colleague, Astley Cooper."

Again, when Tyrrell submitted to him the first volume of his edition of his lectures in 1824, Astley Cooper sends the following letter—

"DEAR SIR,

"I have looked over the manuscript of my Lectures on Surgery. It contains a faithful account, which for forty years I have been endeavouring to learn, and of the practice which for thirty-two years I have been in the habit of teaching in that school, which is proud to rank amongst its Lecturers on Surgery the names of Cheselden Sharp, Warner, Else, and last, although not least, of my most able and judicious preceptor and predecessor Mr. Cline.

"Yours very truly,

"ASTLEY COOPER."

Astley Cooper had a profound belief in seeing the work of others and listening to their teaching, and a man who does this cannot be said to ignore the efforts of fellow-labourers. The visit to Edinburgh was the first evidence of this. Then he visited Paris several times and knew Larrey, Dubois, Desaret, and Chapot. Larrey visited Guy's with Cooper and Dupuytren and saw Key perform lithotomy. Dubois was a spectator at the ligature of the carotid. In Germany and Holland he made the acquaintance of the leading surgeons and examined their collections.

He had a discussion with Hey of Leeds on a point in the anatomy of the parts concerned in hernia. To settle the question he invited Hey to London and provided a subject for dissection, with the result that the visitor was convinced of the

correctness of Cooper's findings. Nothing could have been more friendly and open-minded.

In his participation in discussion at societies Astley Cooper showed his readiness to submit his observations or the result of his operations to criticism. This was particularly noticeable at the Medico-Chirurgical Society, where he described his cases of ligature of the carotid and also that of the aorta.

"Astley Cooper," writes his biographer, "gained the confidence of every medical practitioner who had access to him. This did not originate from his published works or his lectures, but from his innate love of his profession, his zeal in all that concerned it, and his honest desire, as well as great power, in conveying an opinion without exposing the ignorance of another."

#### RETIREMENT FROM GUY'S AND TEMPORARY RETIREMENT FROM PRACTICE

After the death of their adopted daughter in 1814, Mrs. Cooper resided at Gadesbridge, an estate purchased in 1811. Here Astley Cooper spent his spare time, and in the season entertained shooting parties. He moved from the city to New Street in the West End in 1815, partly to save the frequent journey to this part of the town, and also to enable him to get morning exercise in the parks either by walking or riding. He also began to find the excessive demand of the city practice too exhausting. I have referred to the injurious effect of the strain resulting from the effort demanded by the lectures on Comparative Anatomy in the year 1815. It is obvious that little time could be spared for country pursuits. Though only forty-seven he had grown stout in spite of living carefully. He did not relax his daily investigations in the work-room, where he continued to employ an assistant and a draughtsman. His nephew, Bransby, with his wife, joined him in New Street and remained till 1827, when he temporarily retired.

Towards the end of 1824 his attacks of giddiness became more frequent and were attended with difficulty in breathing, but after a few days at Gadesbridge he would quickly recover.

Attributing this increase to the strain of lecturing, he relinquished the lectures on anatomy and confined himself to those on surgery. In January 1825 he sent in his resignation of his lectureship to the governors of St. Thomas's Hospital.

At the request of the students he delivered a few lectures after this date, but refused a similar request in 1830. In doing so, he gratefully acknowledged the high compliment, having

instructed the grandfathers and fathers of many of those who made the request.

He spoke of the folly of not using forbearance in the gratification of ambition, and of the duty men advanced in life are under to make way for teachers, who have the advantage of possessing the vigour and energy of youth. At the same time he resigned the surgeoncy to Guy's, which he had held for twenty-five years, and at the suggestion of Mr. Harrison, the Treasurer, became Consulting Surgeon at the age of fifty-seven.

He spent much more time at Gadesbridge with great improvement to his health. But he did not remain inactive while there, for he embarked on farming operations, and bought young horses, which he trained and improved. Moreover, one of his greatest interests was in treating the various maladies, to which horses are liable. Others sent their horses to him through the local blacksmith once a week, when Sir Astley would remove a corn from the foot or drain an abscess.

Here he kept a dissecting room, and made many preparations, using the irrecoverable animals for any experiment to elucidate a subject on which he was engaged.

His practice in New Street continued to be almost as extensive as when in the city, and in 1826 he was attending the King, the Duke of York, Lord Chatham, and many holding the most prominent positions in the kingdom.

Lady Cooper died from erysipelas of the head in June 1827, and though Sir Astley resumed practice, he found that this was so interrupted by the attacks of giddiness, necessitating frequent absence, that in September he decided to retire from practice, and give himself up to a country life. Having completely recovered his health, he began to suffer for the first time in his life from *ennui*, and he yearned again for his professional occupation.

After a few months he returned to London and took a lodging, intending to see a few old patients on three or four days in the week. His return becoming known, his advice was eagerly sought, and to meet the demand he purchased a lease in Dover Street and set up an establishment. This proving inconvenient, he moved into Conduit Street, where he remained till his death fourteen years later.

In July 1828 he married the sister of an old acquaintance, and the same year was appointed Serjeant Surgeon to George IV.

Such appears to be the true account of his temporary retirement and resumption of practice. It was not due, as has often been said, to any loss of his fortune.



It was during this period, in 1836, that he was a second time elected President of the College, the first being in 1827, the year in which he temporarily retired after the death of his wife.

It is also worth noting that the first volume of the *Guy's Hospital Reports* was published in 1836, eleven years after his resignation of the surgeoncy, and that to this issue he contributed an important paper.

#### THE MAN

One cannot do better than quote two appreciations by men who knew him and his work.

Dr. Pettigrew, in his *Medical Portrait Gallery*, thus describes the overpowering influence Sir Astley Cooper had upon his pupils: "I can never forget the enthusiasm with which he entered upon the performance of any duty calculated to abridge human suffering. This enthusiasm, by the generosity of his character, his familiar manner, and the excellence of his temper, he imparted to all around him, and the extent of the obligations of the present and of after-ages to Sir Astley Cooper, in thus forming able and spirited surgeons, can never be accurately estimated. He was the idol of the Borough School. The pupils followed him in troops; and like to Linnæus, who has been described as proceeding upon his botanical excursions accompanied by hundreds of students, so may Sir Astley be depicted traversing the wards of the hospital with an equal number of pupils listening with almost breathless anxiety to catch the observations which fell from his lips. But on days of operation this feeling was wound up to the highest pitch. The sight was altogether deeply interesting; profound silence obtained upon his entry, that person so manly and so truly imposing, and the awful feeling connected with the occasion, can never be forgotten by any of his pupils. The elegance of his operation, without the slightest affectation, all ease, all kindness to the patients, and equally solicitous that nothing should be hidden from the observation of the pupils, rapid in execution, masterly in manner, no hurry, no disorder, the most trifling minutiae attended to, the dressings generally applied by his own hand, the light and elegant manner in which Sir Astley Cooper employed his instruments, always astonished me, and I could not refrain from making some remarks upon it to my late master, Mr. Chandler, one of the surgeons to St. Thomas's Hospital. I observed to him that Sir Astley's operations appeared like the

graceful efforts of an artist in making a drawing. Mr. Chandler replied: 'Sir, it is of no consequence what instrument Mr. Cooper uses; they are all alike to him, and I verily believe he could operate as easily with an oyster-knife as the best bit of cutlery in Laundry's shop.' There was great truth in this observation. Sir Astley was at that time certainly one of the best operators of the day, and this must be taken in its widest sense, for it is intended to include the planning of the operation, the precision and dexterity in the mode of its performance, and the readiness with which all difficulties were met and overcome."

The second is from William Roots, who was a dresser to the resigning surgeon, William Cooper, and was taken over by Astley Cooper on his succeeding to the surgeoncy.

"From the period of his appointment to Guy's until the moment of his latest breath, he was everything and all to the suffering and afflicted. His name was a host, but his presence brought confidence and comfort; and I have often observed that on an operating day, should anything occur of an untoward character in the theatre, the moment Sir Astley Cooper entered, and the instrument was in his hands, every difficulty was overcome and safety generally ensured."

No doubt reference is here made to the fact recorded by Sir Astley Cooper himself as follows: "I was always of opinion that Mr. Cline and I gained more reputation at the hospitals by assisting our colleagues than by our own operations, for they were always in scrapes, and we were obliged to help them out of them."

Travers, an apprentice, who lived with Sir Astley and became surgeon to St. Thomas's, writes—

"Close and accurate observation, correct and forcible description, and an unwearied industry in the pursuit of discovery, were his peculiar characteristics, and all these, from the new channel into which his labours were now directed, were called into requisition."

Tyrrell, one of his apprentices and subsequently a surgeon to St. Thomas's and the editor of the *Lectures on Surgery*, thus writes of his master, with whom he resided for several years—

"He was in the habit of visiting it (the hospital) at any unoccupied interval, in addition to his regular days of attend-

ance. He would look at particular or urgent cases, before and after lecture, and he generally went round, *à loisir*, as a florist would visit his parterre, with two or three elder students, on a Sunday morning. His interest in his profession was genuine, independent of the additional incitement of the love of reputation or of gain. This was equally evinced in the dissecting room, and in the wards of the hospital: of the two, I should say, his passion was for minute anatomy.

"I may observe that he was distinguished, at the time of which I am speaking, by an untiring energy of character, and the faculty of communicating his opinions and his ardour by conversation with the young men around him. He tried to elicit remarks from them with remarkable earnestness, nor did he often fail to excite a disposition on their part to meet his wishes.

"The simplicity of his habits and mode of living were in perfect keeping with the activity of a mind which was intently bent upon great objects. He rose and generally retired early, nor did he allow his toilet to occupy much of his time. His meals were quickly dispatched, and though he ate heartily, he never drank anything but water at dinner, and rarely exceeded two glasses of port wine after. He had a Spartan contempt for self-indulgence at table, and used to say he could digest anything but sawdust."

In a piece of autobiography Astley Cooper thus writes of himself—

"Sir Astley Cooper was a good anatomist, but was never a good operator where delicacy was required. He felt too much before he began ever to make a perfect operator.

"For the operation of cataract he was quite unfitted by nature.

"Quickness of perception was his *forte*, for he saw the nature of disease in an instant, and often gave offence by pouncing at once upon his opinion.

"The same faculty made his prognosis good.

"He was a good anatomist of morbid, as well as of natural structure.

"He had an excellent and useful memory.

"In judgment he was very inferior to Mr. Cline in all the affairs of life, and hence was continually walking upon a mine ready to explode under his feet. His imagination was vivid, and always ready to run away with him if he did not control it.

"His strength consisted in the quickness with which he

could decide upon the nature of a case, and the certainty almost of his decision being right, as well as the readiness with which he adapted his means of treatment. His diagnosis was really most remarkable. He obtained that decision from having made it a practice, when young, to see all the poor who would come to him, and thus he saw such a variety of disease as to make him as familiar with it as a parent with his child.

“His principle in practice was, never to suffer any one who consulted him to quit him without giving them satisfaction on the nature and proper treatment of their case.”

I have spoken of his industry, which never relaxed until illness laid hold of him in the year of his death. Of himself he writes, at a period when he was Cline's assistant—

“I went to the hospital before breakfast to dissect for lecture. I injected three subjects. I lectured from two o'clock till half-past three. In the evening three times per week, I lectured on surgery. I attended to the interesting cases in the hospital, making notes of them, and in this latter practice I always persevered.”

#### CONCLUSION

Astley Cooper died in 1841 at the age of seventy-four, having extended and upheld the reputation of British surgery for half a century. He was buried beneath the chapel of the hospital he loved so well, and whose fame he did so much to extend. By his will he founded a triennial prize, and it is significant that he directed that the first subjects for inquiry should be upon the thyroid, the spleen, the thymus, the suprarenal capsules, and the state of the blood and blood-vessels in inflammation, all subjects on which he had himself made observations and conducted experiments. He foresaw that future workers, better equipped, would unravel the secrets which had baffled him.

In concluding this account of a great surgeon and one of the most brilliant of Guy's men of any time, I shall quote the last paragraphs of my *Hunterian Oration*, which was delivered before the Council of the Royal College of Surgeons in February 1921 as the best tribute I can offer.

“The Hunterian era awoke in the minds of men a desire to explore the old ground by new methods and to unearth the truths so long concealed. There was a spirit of adventure, like that which animated the Elizabethan explorers, the ambition of the healthy human intellect to extend its range of vision and knowledge.

“To Hunter belongs the credit of the discovery of this new

world. He it was who lighted the torch, and I hope I have shown that Astley Cooper was amongst those who first carried it forward in the race, kept it alight, and then passed it on, not only undiminished, but burning with a brighter flame; and so when his course was run the goal was nearer for the part he had taken."

*"After brief life men die, and like runners in a race hand on their torch to another."*

# A DISCUSSION ON ADDISON'S (PERNICIOUS) ANÆMIA

AT THE GUY'S HOSPITAL MEDICAL RESEARCH CLUB ON  
JANUARY 12, 1921

## I. INTRODUCTION

By SIR WILLIAM HALE-WHITE, K.B.E., M.D.

IN the first half of the nineteenth century some authors recorded cases of the condition which was later called pernicious anæmia, but did not recognise it as a distinct disease. This was first done by Addison<sup>1</sup> in a paper read before the South London Medical Society in 1849. He called it "idiopathic anæmia," but later the name "pernicious anæmia" was applied to it. Both are unfortunate terms, and it would be better to call it Addison's anæmia. This name would have come into general use, were it not that confusion might arise with the malady known as Addison's disease. Between 1849 and 1855, when Addison described "idiopathic anæmia" in his famous work on *Diseases of the Suprarenals*, it had become well known in Guy's Hospital and in London, and Wilks, who was the first to examine the blood in this disease, had shown that leucocythæmia was not present. The cases that have occurred in this hospital have been described in the *Guy's Hospital Reports* by Wilks,<sup>2</sup> Taylor,<sup>3</sup> Pye-Smith,<sup>4</sup> and myself.<sup>5</sup> Hopkins<sup>6</sup> in the same publication in 1893 gave a full account of the distribution of iron in the liver and other organs, and he described the changes in the urine. French<sup>7</sup> has written the article on pernicious anæmia in Clifford Allbutt and Rolleston's *System of Medicine*. We may therefore claim that in this Medical School the disease has been both discovered and carefully studied.

Several years after the discovery of "idiopathic anæmia" here, the Germans, being ignorant of the English literature, rediscovered it for themselves, but Wilks and Pye-Smith were easily able to show that we were first in the field, and this fact has been recognised both in France and America. The Germans, moreover, confused matters, for some of their cases were examples of severe secondary hæmorrhage.

Since Addison's original description other facts have been discovered. He described the pallor as waxy; it is now

recognised that lemon colour more correctly indicates its tint. Microscopical examination of the blood was in his day in its infancy; now definite alterations in the blood are given as characteristic; for my own part I believe that the statements in the text-books are too dogmatic. Thus it is said that the colour-index is above unity, and the chart given as typical in Osler's "Text-Book" shows it above unity on every examination. It is not always so; in the same patient it may sometimes be above, sometimes below this, even during the same day, and I consider that it is rash to deny a diagnosis of pernicious anæmia because a simple examination of the blood shows a colour-index below unity.

Addison had no clinical thermometer and was therefore unaware that the temperature is usually slightly raised—a remarkable thing, for we should expect the profound anæmia to lower oxidation; indeed the anæmia immediately following profuse loss of blood is accomplished by a subnormal temperature. He had no ophthalmoscope and was unaware of the presence of retinal hæmorrhages and slight retinitis. I remember a man in John Ward, in whom an ophthalmoscopic examination alone led to a prediction of pernicious anæmia, which proved to be correct. Addison does not mention the urine; we now know that, although variable in colour, yet sometimes it is characteristically the colour of dark sherry. A full account of this will be found in Hopkins's article in the *Guy's Reports* for 1893.

There were not in 1849 the means we possess of examining the gastric juice; now we are aware that hydrochloric acid is absent from it in pernicious anæmia. The significance of this we shall hear about in this debate. Addison does not refer to gastro-intestinal symptoms, but we have learnt that they are frequent. In the series of cases published in the *Guy's Hospital Reports* for 1890, it was shown that diarrhœa and vomiting are common, quite apart from the taking of arsenic. At one time it was suggested that pyorrhœa was the cause of pernicious anæmia, but I should not say it was more often seen in sufferers from this disease than in others, and I have met with patients afflicted with pernicious anæmia whose mouths were quite healthy.

About fifteen years ago there was under my care in the hospital a patient suffering from this disease, who showed brown spots in the mouth, indistinguishable from those seen there in disease of the suprarenals, and in whom they were not due to arsenic.<sup>8</sup> Others have since seen them in similar cases, but they are very rare.

Addison did not examine the bones; now we know that the

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marrow is very often abnormal. So many cases have been recorded, however, in which it is stated to be normal, that it would be of interest to hear if this is possible; my own impression is that the marrow is always abnormal.

Addison was unaware of the degeneration of the spinal cord. There is in the Guy's Museum an excellent specimen of this condition from a patient sent in as an example of anorexia nervosa; we found an extensor plantar reflex, and immediately examined the blood; we found she had pernicious anæmia. She died in a few hours, and the autopsy showed we were correct. I hope we may get some hint as to why this degeneration occurs.

That free iron may be found in the liver and other organs was unknown when the disease was first described. Lastly, it was not known that either arsenic or transfusion was beneficial.

Addison gives a very gloomy prognosis, saying, "With perhaps a single exception the disease, in my experience, resisted all remedial efforts, and sooner or later terminated fatally." This is our present experience, but once I followed up some cases and found one patient still alive twelve years and one four years after the original diagnosis had been made.

Arsenic will benefit for a time, but sooner or later the patients die; it may be after two, three, or four relapses. It will be of interest to hear opinions as to the relative value of arsenic by the mouth and intravenously, and also whether transfusion is of more than temporary benefit. Certainly many patients who have been transfused have ultimately died, but that may be because it has only been used in severe cases.

I would suggest that the disease is one of blood destruction by an unknown agent; that probably, considering the frequency of gastro-intestinal symptoms and the large amount of free iron in the liver, the destruction takes place in the portal area; that the changes in the marrow and some of the alterations in the blood indicate an attempt to compensate for this excessive destruction; and that the yellow colour of the skin and the occasional dark urine are perhaps symptomatic of the destruction of the blood.

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## II. THE ESSENTIAL FACTOR IN THE PATHOGENESIS, DIAGNOSIS, AND TREATMENT OF ADDISON'S ANÆMIA

By A. F. HURST, M.D.

### *Nomenclature*

I SHOULD first like to say a few words on nomenclature. In 1849 Addison gave the first description of the disease we are discussing to-day and called it "Idiopathic Anæmia." Twenty-three years later Biermer published his work on the same subject, and called the disease "Pernicious Anæmia," and ever since it has been known in Germany as "Biermer's Anæmia" with equal frequency. But beyond the pernicious name he invented, Biermer added little but confusion to our knowledge of the subject, and as the disease is neither idiopathic nor necessarily pernicious, there can, I think, be no doubt that "Addison's Anæmia" is for every reason the most satisfactory name.

### *Pathogenesis*

It is now generally agreed that Addison's anæmia is caused by a hæmolytic toxin produced by some infection in the alimentary canal. I believe that this infection cannot take place unless free hydrochloric acid is completely absent from the gastric contents. In the Guy's cases this is a rule without exception. Dr. P. N. Panton tells me that at the London Hospital achlorhydria has also always been found, with the single exception of one recent case. Owing to the fact that the diagnosis can never be regarded as absolutely certain until after an autopsy has been performed, this one exception out of some fifty cases is of small importance, and it may very well prove to be due to a mistake similar to that made in the only two cases at Guy's in which during life achlorhydria was not found, but in which after death a different cause was discovered for the anæmia. These results agree with those obtained by Cabot<sup>1</sup> in a series of seventy-nine cases and by Carr<sup>2</sup> in fifty-seven cases, in which achlorhydria was present in over 90 per cent., and, if mistakes in diagnosis are excluded, probably in 100 per cent.

There is a good deal of evidence to show that the achlorhydria precedes the development of the anæmia. The digestive symptoms, which are present in a large proportion of cases, are of a kind which may well be caused by achlorhydria, and there is frequently a history that these have been present for many years, as Robert Hutchison<sup>3</sup> pointed out in 1909. Moreover,

the achlorhydria is complete, however early the case may be, whereas all the other symptoms develop gradually, none of them being present constantly from the onset. Although the blood changes and other symptoms show definite remissions, free hydrochloric acid is still found to be absent, even if a patient is examined in one of the periods of apparently complete remission. We have had one striking case of this kind at Guy's. Lastly, in other severe anæmias, so far as my experience goes, achlorhydria is not present. Consequently the achlorhydria cannot be regarded as a result of the disease: it is neither caused by the same toxins as those which produce the anæmia, as is probably the case with the spinal cord changes, nor is it secondary to the anæmia like the circulatory symptoms. I believe that it is, in fact, the essential predisposing factor, which has probably in most cases been present for years and may indeed be congenital, as Ryle and Bennett<sup>4</sup> have shown that about 4 per cent. of healthy young men have achlorhydria.\* Sometimes it may have been acquired as a result of chronic gastritis, especially that caused by alcohol, or as a result of a gastro-enterostomy as in a Guy's case observed by Dr. Conybeare, or total gastrectomy as in a case at the Mayo Clinic and perhaps another of Moynahan's. The achlorhydria allows the bacteria, which produce the hæmolytic toxins, and which probably have their primary focus in the mouth, to pass through into the intestine without being destroyed in the stomach by the hydrochloric acid which ought to be present.

### *Diagnosis*

For years I have taught that a provisional diagnosis of Addison's anæmia can generally be made on Addisonian lines, without the aid of any modern methods of clinical investigation. If a patient suffering from the ordinary symptoms of anæmia has the characteristic lemon-yellow colour, it is extremely probable that he is suffering from Addison's anæmia. If digestive symptoms are present, the diagnosis becomes more probable, and the addition of symptoms of early subacute combined degeneration of the spinal cord would make it almost certain. The most important confirmatory evidence is in my opinion not hæmatological, but is the discovery after a fractional test-meal of complete achlorhydria. If free hydrochloric acid is present, the diagnosis can, I believe, be rejected with certainty. The blood examination is less important, as the characteristic

\* Since this was written Valdemar Bic (*Lancet*, i. 631, 1922) has published a case in which achylia gastrica was known to have been present for twelve years before the onset of the anæmia.

changes are not often present throughout the disease. As Sir William Hale-White has already pointed out, the colour-index is often under 1 for long periods, and I am convinced that the current teaching that Addison's anæmia must not be diagnosed unless the colour-index is over 1 is unjustified. I doubt very much whether any importance at all can be attached to such slight variations from 1 as 0·9 and 1·1, particularly as the rule that the colour-index is always over 1 in Addison's anæmia dates from a time when the hæmoglobinometer and hæmatocytometer in common use were so badly standardised that different instruments might give a colour-index of 0·8 and 1·2 respectively in the same patient at the same time. Even now it requires an unusual degree of experience to estimate the colour-index so accurately that the error is less than 0·1. With regard to the presence of megaloblasts it is generally acknowledged that these can often only be found after prolonged research frequently repeated over a long period, so that their absence on ordinary examination is of small importance, however valuable their discovery may be as positive evidence. I should be quite prepared to diagnose Addison's anæmia with a colour-index well below 1 and in the absence of megaloblasts in a lemon-yellow patient with complete achlorhydria and with the signs and symptoms of subacute combined degeneration of the cord, for I would know that, if hæmatological examinations were repeated day after day, perhaps for several weeks, characteristic changes would eventually appear, though possibly only temporarily—but why wait all these weeks before making a diagnosis and instituting the appropriate treatment?

#### *Treatment*

In discussing the treatment of Addison's anæmia it is essential to distinguish between the treatment of the anæmia and the treatment of what has caused the anæmia. The anæmia generally responds rapidly to arsenic and to repeated transfusion, but neither of them has any permanent effect, because they do not touch the cause. All obvious foci of infection must, of course, be eradicated, and in this connection my experience does not agree with that of Sir W. Hale-White, as I should have said that oral sepsis is present or there is evidence of its former presence in almost every case. The secondary infection of the bowel must then be dealt with, and I think that nothing helps in this more than the continual administration of large doses of dilute hydrochloric acid with pepsin at every meal. This has often been tried before in the active stage of the disease, but so far as I know no emphasis has been laid on the great importance

of giving it during the quiescent periods, and, in cases of apparent recovery, for the rest of the patient's life, or at any rate so long as a fractional test-meal shows that there has been no return of free hydrochloric acid, such as might occur if the achlorhydria was secondary to chronic gastritis. I advise every patient to continue in this way with the acid treatment, and to have a blood examination made every three months, so that he may have a renewed course of arsenic and, if necessary, another transfusion as soon as any sign of returning anæmia is discovered.

It seems to me that a full recognition of the fundamental part played by achlorhydria in the production of Addison's anæmia will more than anything else lead to the realisation that the disease is no more pernicious than any other form of secondary anæmia.

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## III. CHARACTERISTICS OF THE BLOOD IN ADDISON'S ANÆMIA

By E. W. BOWELL.

## I

THE film contains red corpuscles of various sizes, some being smaller than the average, others larger. Associated with this is an irregularity of shape, flask-shaped forms being frequently seen.

(a) This is liable to happen in all anæmias; but in other cases than Addison's anæmia it is generally found that the larger corpuscles are paler than the normal-sized ones, while in Addison's anæmia they may even take a deeper stain. As the eosin, which is used to stain them, is said to be a "specific stain for hæmoglobin," it is usual to estimate the amount of hæmoglobin present by examining the depth of staining. As a matter of fact, however, the specificity of eosin in this particular is shared by nearly all other acid dyes, and it is probably more a measure of the reaction of the corpuscle than anything else.

(b) In close connection with the last character we also observe that the eosin stain tends to be confined to the margin of the red corpuscle. This is to be carefully distinguished from the pseudo-marginal staining which is seen in ordinary cases of

hæmoglobin deficiency; in these the light centre is gradually shaded away from the colour of the margin, which is itself less definite than that of a normal eosin-stained red corpuscle, while in Addison's anæmia the margin is more deeply stained than normal. But in criticism of this marginal staining it must be noted that it is never seen so well as in specimens fixed by heat; and that it may be produced artificially by heat and by certain other methods of fixation in normal blood.

(c) In cases where there is no question of abnormal tendency to hæmolysis, the red corpuscles vary very much in their fragility. If the film is not taken in the best way, anisocytosis and poikilocytosis will certainly appear in some part of the preparation, owing to the destruction or mutilation of some of the corpuscles. It is sometimes a real difficulty to distinguish between this artefact phenomenon and the pre-existing variety, characteristic of Addison's anæmia; if, however, there is to be found anywhere on the film a patch of well-spread normal corpuscles, it is improbable that the case is true Addison's anæmia. In the latter the fragility is probably actually much less than in normal blood; at least it has always seemed so to me. A badly taken film in Addison's anæmia may show very few large corpuscles, as these naturally have the greatest tendency to break up.

(d) In quite normal blood there is more variation in the size of the red corpuscles than is generally imagined. It is on account of this that some specimens of normal blood film very badly, the regularity of the film depending actually upon its containing a large number of units of approximately the same size. Also, in normal blood there is a physiological and periodic variation in the diameter of the average corpuscle. I wish to lay some emphasis on the fact that if a thin film is not taken and then immediately dried (as by vigorous shaking), no correct measurements of the size of the corpuscles can be made. Some authors propose to measure wet preparations; but the diameters of the corpuscles in wet preparations do not remain constant.

(e) My own view is that the degree of plasticity or fragility of the red corpuscles is very largely a matter of individual idiosyncrasy; and I am inclined to think that it varies with the serological group to which each individual belongs.

## II

The film contains few (usually very few) platelets, and those which occur are larger and less regular in size than normal platelets.

The platelets are almost certainly derived from the red

corpuscles by breaking down. Their absence, therefore, confirms the opinion already expressed as to the lesser degree of fragility in Addison's anæmia. They are also important morphological factors in the process of clotting, and this, as has frequently been observed, is slow in Addison's anæmia, as conversely they are undoubtedly more common in those conditions, in which clotting is more rapid than normal and may even take place *intra vitam*.

### III

The film contains nucleated red corpuscles, of which a majority are megaloblasts.

This is undoubtedly the case in those films which may unhesitatingly be labelled Addison's anæmia. But all writers on the subject agree that sometimes very few megaloblasts may be present; some add that they occur in greatest numbers at the crises of the disease. Some would make the discovery of a single megaloblast the occasion for a positive diagnosis. To me it seems that there are often nucleated red cells in a film which might or might not be megaloblasts; and I have had the opportunity lately of seeing a good many films unusually rich in nucleated red cells. Megaloblasts are normally replaced by normoblasts at quite an early stage in foetal life; and it is quite unusual (so far as I have investigated) to find in foetal blood those curious dividing nuclei which are seen in many cases of advanced anæmia. There are also nucleated red corpuscles which can be distinguished with great difficulty (if at all) from imperfectly formed neutrophile leucocytes; and some of these are certainly megaloblasts. I am therefore inclined to think that the presence of megaloblasts in Addison's anæmia is due to the same cause which makes the neutrophile leucocytes in that disease more scanty than in normal blood, and frequently ill-formed and with smaller nuclei than the normal neutrophiles. It seems to me that this is more probable than the theory that the bone-marrow on this occasion goes back to the manufacture of an exceedingly antiquated type of red corpuscle.

### IV

In Addison's anæmia there are seen many curious modifications of red corpuscles, which may be coloured uniformly or in patches by the basophile element in the staining mixture. It is not worth while to enumerate all the names which have been applied to these cells; there is no agreement as to their significance, though it is at first sight probable that they are

modifications of the process which yields the nucleated red corpuscles. It cannot be claimed that any of them is exclusively characteristic of Addison's anæmia. But they are not often seen in films in which there are many platelets.

## V

In Addison's anæmia the total leucocyte count is low, and there is a deficiency of neutrophile corpuscles, those present, as already mentioned, being frequently defective examples.

I think this is a really important point. If one took ordinary blood and removed about half of the neutrophile cells, the total and differential count of the remainder would be similar to those of Addison's anæmia. The neutrophile corpuscle is one of the most valuable things in the body; it is possible that its deficiency may bring about some of the nervous or other symptoms characteristic of Addison's anæmia. In fact, if all anæmias were to be classified anew, I should put on one side those in which the number of neutrophile cells per cubic millimetre is definitely low. In most of the secondary anæmias there is a neutrophile leucocytosis, both actual and relative. In leukæmia we find a similar defect of neutrophile cells, for there is no reason to suppose that myelocytes can officiate as neutrophiles, and probably the normal termination of myelocytic leukæmia is that it becomes a myelogenic (or lymphoidocytic, incorrectly called a large-celled lymphatic) leukæmia. Addison's anæmia is not a common disease; this at least fits in well with the fact that while most people have a normal supply of neutrophile cells, which enable them to react normally to many diseases, there is a minority who are from childhood deficient in them, tending to make small lymphocytes instead, and thus retaining an ancestral disability, which is still found in the six-months foetus, as it is in most lower primates, which have notoriously small power of resistance to diseases caused by micro-organisms. I suggest that it is this minority which is liable to develop Addison's anæmia. But when a secondary anæmia, which is associated with a large production of neutrophile cells, has lasted a long time, signs of exhaustion are always manifested. In this way the aplastic anæmias arise; they may be clinically identical with Addison's anæmia, while the blood examination shows (as I think) that they have arrived at the same condition by a different route.

## VI

The colour-index is no doubt typically high in Addison's anæmia; but our methods of obtaining this figure are by no

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means perfect, and in any case the high colour-index is only another way of stating that there are many large red corpuscles (I).

### VII

There is a diminution in the number of the red corpuscles—a character of all anæmias.

## IV. ACHLORHYDRIA AND DIGESTIVE SYMPTOMS IN ADDISON'S ANÆMIA

By J. A. RYLE, M.D.

HAVING interested myself in the clinical symptoms which may be found to accompany achylia gastrica—better termed achlorhydria—as encountered in the routine investigation of dyspeptics, I thought that it might be of interest to compare these with the symptoms recorded in the case-histories of patients suffering from Addison's anæmia. For this purpose I have referred to the analysis by Dr. Herbert French of sixty-eight consecutive cases of "pernicious anæmia" in the *Guy's Hospital Reports* for 1909.

The symptom, found in cases of achlorhydria may be roughly divided into three groups—gastric, intestinal, and general. The gastric symptoms are usually vague and consist for the most part of epigastric discomfort or fulness, which seldom amounts to actual pain, though occasionally the symptoms of duodenal ulcer may be simulated. More characteristic is nausea, experienced especially in the morning, with which we are most familiar in the case of the chronic alcoholic, and, more rarely, vomiting.

Diarrhœa is the leading intestinal symptom, which, in the absence of any history of dysentery or of other evidence of an ulcerative bowel lesion, becomes one of the most important diagnostic symptoms of achlorhydria. Gastrogenous diarrhœa has a tendency to occur especially after meals, and is not usually associated with the urgent bowel discomforts of an enterogenous diarrhœa.

The general symptoms accompanying achlorhydria are very vague and amount to little more than a general lassitude and hypotonus, together with those features usually referred to under the heading of intestinal toxæmia.

Now as to the frequency of these and other gastro-intestinal symptoms in the cases in Dr. French's series. Forty-five



out of sixty-eight consecutive cases had a definite record of gastro-intestinal symptoms, including diarrhœa, vomiting, bilious attacks, etc. Of these forty-five no less than twenty had chronic or recurrent diarrhœa, which I have referred to as a very important diagnostic symptom in achlorhydria. Seven patients had symptoms dating back for five years or more before the onset of the anæmia. Thus Case 5, aged 57, had a history of abdominal pains and diarrhœa since the age of 13; Case 7, aged 44, had suffered from diarrhœa since the age of 19; Case 8, aged 51, had had attacks of diarrhœa since he was 25; Case 11, aged 56, had diarrhœa with blood starting five years before the first anæmia; Case 17, aged 50, had diarrhœa starting seven years before; Case 36, aged 32, had diarrhœa starting seven years before; and Case 38 said his "bowels were loose ever since he could remember."

These histories and clinical manifestations, therefore, seem to supplement the laboratory finding that achylia is an important feature of Addison's anæmia and to support the theory that it very likely precedes the development of the anæmia.

## V. ACHYLIA GASTRICA IN ADDISON'S ANÆMIA

By A. W. M. ELLIS, M.B., Toronto, Assistant Director, Medical Unit,  
London Hospital.

It is to me a great pleasure and privilege to be present at this discussion of Addison's anæmia in Addison's old hospital. It is surprising how little has been added to our knowledge of the disease since the original description by Addison. The most important contribution since that time has been perhaps the demonstration of the almost constant association of achylia gastrica with this type of anæmia, and it is on this point that I should like to touch briefly.

My colleague, Dr. Maitland-Jones, has just finished reviewing the cases of Addison's anæmia admitted to the London Hospital since 1910, about one hundred and thirty in all. Gastric analysis had been done in thirty-six of these, and of these thirty-six, in only one was free hydrochloric acid present, and in this patient the diagnosis was open to grave doubt.

In a recent paper in the *Johns Hopkins Hospital Bulletin*, Levine and Ladd reported the results of gastric analysis in one hundred and seven cases of Addison's anæmia. In only one definitely accepted case was free hydrochloric acid present. In one patient the anaçidity was discovered and recorded three years before any evidence of anæmia made its appearance.

Levine and Ladd consider the alteration in gastric secretion an even more constant phenomenon of the disease than the typical blood changes.

A point of clinical interest, which has not been mentioned this afternoon and which was noted by both Maitland-Jones and Levine and Ladd, was the great frequency of grey and white hair in this condition.

## VI. THE CHANGES IN THE SPINAL CORD IN ADDISON'S ANÆMIA

By C. P. SYMONDS, M.D.

IN connection with the pathological changes occurring in the spinal cord in cases of Addison's anæmia I think we should be careful to avoid the use of the term "sclerosis," since this is an inaccurate description of the microscopical picture. Actually there is no such increase of the neuroglial elements as occurs in tabes and disseminated sclerosis. The cord is therefore not shrunken as it is apt to be in these diseases, but is of a normal size and may even appear slightly swollen.

The pathological process appears to begin with degeneration of the nerve fibres, both myelin sheaths and axis cylinders, and this is manifested earliest in the centre of the posterior and the lateral columns at about the mid-dorsal level. There are none of the changes in or around the blood vessels which we are accustomed to find in inflammatory lesions of the central nervous system.

So far, therefore, as we can judge from the histological picture, the morbid process is one of primary degeneration, and the term "sub-acute combined degeneration" would seem to be the most appropriate title for the disease. The condition may occur in the course of other illnesses, such as the cachexia of malignant disease and the leukæmias, but is only rarely found in such circumstances, being almost always associated with Addison's anæmia.

It is of interest to note in these latter cases that in a number of instances, in which the progress of the disease has been carefully followed from its earliest symptoms to the fatal termination, the signs and symptoms of the affection of the spinal cord have definitely preceded any abnormality in the blood picture.

On the other hand, there are the cases in which signs of nervous disease first make their appearance some time after

it has been possible to make the clinical diagnosis of Addison's anæmia on other grounds.

It would seem therefore that the combined degeneration cannot be secondary to the Addison's anæmia, but that both result from injury by some unknown poison with a selective incidence upon spinal cord and bone marrow. It is perhaps of interest to note that combined degeneration of the posterior and lateral columns also occurs in ergotism, pellagra, and lathyrism—diseases which are all related to disturbances of gastro-intestinal origin.

As to the frequency of nervous symptoms in the case of Addison's anæmia, there is considerable diversity of opinion. Neither Addison himself, nor the other earlier writers upon pernicious anæmia, made mention of nervous symptoms; and the recognition of the characteristic clinical signs resulting from sub-acute combined degeneration dates only from the beginning of the present century.

The signs in many cases are of a trivial nature in comparison with the severity of the general illness and may readily be missed by one who is not on the look-out for them. It is important to inquire in every case for the earliest symptoms, which as a rule take the form of paræsthesiæ in the extremities—tingling, pins and needles, or numbness in the feet and in the finger tips, somewhat resembling those complained of in cases of polyneuritis.

When these points are carefully inquired for and a routine neurological examination is made in every case of Addison's anæmia, the percentage of patients showing nervous symptoms appears to be high. Woltmann in 1919 reporting 150 cases of pernicious anæmia from the Mayo Clinic, states that nervous symptoms were present in 80 per cent.

## VII. SOME BIO-CHEMICAL OBSERVATIONS IN ADDISON'S ANÆMIA

By J. H. RYFFEL, M.B.

### 1. *Clotting Time*

A CHARACTERISTIC in Addison's anæmia as distinct from secondary anæmias is that the clotting time is delayed. By Dale and Laidlaw's method the time of clotting is found to be usually about 130 seconds at 37° C. instead of the normal 100 to 110 seconds.

### 2. *The Achylia of Addison's Anæmia*

The achylia of Addison's anæmia is a true achylia in that not only is no free hydrochloric acid developed in the gastric contents, but the contents are not even acid to congo red. In my experience, when a case of marked anæmia does not show achylia, there are also other characteristics which differentiate the case from one of Addison's anæmia.

### 3. *Urobilin in Urine and Fæces*

Sir William Hale-White referred to the occurrence of urobilin in the urine of these cases. This is a variable sign. In some phases it may be well marked, but more commonly it is scarcely more than in the normal, and certainly not as marked as in many other conditions. Excess of the same pigment in the fæces pointing to excessive destruction of blood pigment is probably more characteristic, but the important point is an increased daily output of the pigment, and not a high proportion in a specimen of fæces, as this might be due to constipation.

### 4. *The Effects of Transfusion*

The use of transfusions of blood is analogous to the use of arsenic in that it appears to act merely by stimulating the production of red cells. As a direct result of transfusion an increase in hæmoglobin of 10 per cent. is all that can reasonably be expected. This is followed in some cases by a progressive rise in hæmoglobin, which is difficult to account for, unless one supposes that the transfusion serves to break a vicious circle. In these cases the blood-forming tissues have presumably undergone hypertrophy but are in some way handicapped by the deficiency of hæmoglobin in circulation. A sudden rise in hæmoglobin relieves this disability and blood formation is encouraged.

VIII. THE BLOOD AND GASTRIC JUICE IN  
ADDISON'S ANÆMIA

By E. P. POULTON, M.D.

*The Meaning of a High Colour-Index*

THE results of Dr. Campbell and other workers in this field are in my opinion of great importance, because they give a definite physical meaning to the term "colour-index." This expression indicates whether each individual corpuscle contains more or less than the normal quota of hæmoglobin, according as it is greater or less than unity. There have always been two possible explanations of this fact: (1) that the corpuscles differed in the concentration of their hæmoglobin, and (2) that the corpuscles merely varied in size. We now know that since the "volume-index" and "colour-index" run almost parallel to one another, the colour-index merely expresses the average size of the corpuscle. In Addison's anæmia they are as large or larger than normal, in chlorosis and secondary anæmia they are smaller than normal, because the colour-index is less than unity. However, the colour-index and volume-index cannot be regarded as identical. There are slight differences between them in individual cases, which may be rather outside the limits of experimental error. Such differences may well be due to alteration in the fluid content of the corpuscles, which would alter the concentration of the hæmoglobin slightly, in the same way that other cells of the body no doubt vary from time to time in the amount of fluid they contain. Nevertheless the outstanding fact remains that variations in the colour-index in different diseased states of the blood represents almost entirely variations in the size of the corpuscles.

From this it follows that in the anæmia following hæmorrhage the corpuscles are small, and this no doubt represents the reaction of healthy marrow when called upon to regenerate blood rapidly. The small corpuscles can be formed quicker than large ones, and there is the additional advantage to the organism that with small corpuscles the surface area is increased per unit volume of corpuscular substance. This would facilitate the interchange of oxygen and other substances.

Addison's anæmia, with its large corpuscles, affords a sharp contrast with the preceding condition. We know there is abnormal blood destruction in Addison's anæmia. If the marrow were healthy it would respond with small cells. The cells are large in spite of the anæmia. Hence there must be

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abnormal action on the part of the marrow. It might be argued that there are two independent processes, increased blood destruction and abnormal blood regeneration. It is perhaps safer to assume that one follows the other, viz. that in this type of disease the marrow is primarily at fault, and that the blood destruction follows, because the red cells are made imperfectly.

Chlorosis is a different problem, because here the cells are small and yet there is no blood destruction. It can perhaps be explained on Lorrain Smith's hypothesis that the volume of the blood plasma is increased in this disease. This would be equivalent to an anæmia, and the marrow would naturally respond by producing small cells.

### *The Gastric Juice in Addison's Anæmia*

The relation of anæmia to the hydrochloric acid of the gastric juice is a question that has been debated for years. Strauss reviewed the subject in Von Noorden's *Pathologie des Stoffwechsels* (Vol. I, p. 925) in 1907, and gives twenty-one references to work done on the subject. It seems pretty well established that there is nearly always absence of free hydrochloric acid in the gastric juice in Addison's anæmia and hypochlorhydria in secondary anæmia, while variable results have been obtained in the gastric juice in chlorosis. Two interesting facts are mentioned: (1) that bleeding an animal immediately diminished the hydrochloric acid, and (2) that there was an increase of hydrochloric acid during temporary improvement in a case of pernicious anæmia (Bloch). In this connection mention may be made of a series of cases published by Levine and Ladd in the *Johns Hopkins Bulletin*. As they were much struck with the existence of achlorhydria in pernicious anæmia, they collected "all possible cases of pernicious anæmia" in the Peter Bent Brigham Hospital, to investigate the relationship further.

The large number of cases (143) observed in the course of a few years is remarkable, because, in this country at any rate, Addison's anæmia is not a very common disease. Further, they state that during the period covered by this series of 143 cases, 401 cases of lobar pneumonia were also observed, a very high ratio for the former. Post-mortems were obtained on only 11 cases out of the 107 who died, but no mention is made of the criteria on which the post-mortem diagnosis was based. The colour-index is not given for any of the cases. On looking at the details of some of the cases it is difficult to see why the diagnosis was made. Case 18 would seem much more likely to be one

of cancer of the stomach. Case 36 was seen in 1915, was doing heavy work in 1917, and feels well in 1920. Case 61 had a hæmoglobin percentage of 80 in 1915 and was about the same in 1918. These are a few cases picked out at random. It seems difficult not to imagine that some of the cases may have had anæmia from other causes, and if this is the case the series affords valuable confirmation of the thesis that anæmia itself leads to hypochlorhydria.

There is at present no satisfactory theory of the formation of the gastric juice. If hydrochloric acid is secreted into the stomach, the problem is to find some acid in the blood with which the base formerly combined with the hydrochloric acid can combine. Without such an acid to take the place of the hydrochloric acid it is obvious that the blood would become highly alkaline. Campbell and Joffe and I\* showed that there was a free acid present in the blood, which was capable of taking up comparatively large amounts of base, viz. oxyhæmoglobin. Without going into speculation as to the exact mechanism involved, it seems that this suggestion fits in admirably with the relationship of hypochlorhydria and anæmia.

It is also possible to explain why in Addison's anæmia the effect on the hydrochloric acid secretion is more marked than in secondary anæmia. Since the cells in Addison's anæmia are large, while in secondary anæmia they are small, there is a larger cell surface in the latter case, as already explained. This would facilitate the migration of base into the cells to combine with hæmoglobin and so help in the production of hydrochloric acid. The hydrochloric acid of the gastric juice would not be so much reduced in amount. The two factors, diminution of hæmoglobin and diminution of the size of the cells, act in the contrary direction to one another, one diminishing the hydrochloric acid and the other increasing it. It is possible to imagine a condition in which the second factor predominated, and then the hydrochloric acid might be increased, even though there was anæmia. This might explain those cases of chlorosis in which hyperchlorhydria was found. In other cases where the former factor was predominant the acid would be low. Some support is given to this theory by what has been shown by London and Sokoloff (Von Noorden, *loc. cit.*) to occur when an animal is bled. There is at first a hypochlorhydria, and after two or three weeks a hyperchlorhydria. Then the acid falls to normal. The stage of hypochlorhydria would correspond to the stage of blood regeneration when the blood was receiving large numbers of

\* Joffe and E. P. Poulton: *Journ. Physiol.*, liv. 9, 1920; Campbell and E. P. Poulton: *Journ. Physiol.*, liv. 152, 1920.

small cells, though the percentage of hæmoglobin would still be below normal. Anæmia then leads to hypochlorhydria, but it is possible that some other factor may also be present in Addison's anæmia. It has been known for a long time that atrophy of the gastric mucous membrane occurs in pernicious anæmia. Sophie Herzberg,\* as the result of very careful work, considers that the anæmia is not secondary to the stomach changes, but that both the anæmia and the atrophy may be due to the same cause. One of her cases, who died in about six months, had a normal value for hydrochloric acid in the gastric juice, and the oxyntic cells were not much altered. The cases of long standing that she investigated all had achlorhydria, and there was marked atrophy of the mucous membrane and absence of oxyntic cells.

This whole question of achlorhydria is complicated by the fact that regurgitation from the duodenum, which Boldyreff showed to be a normal phenomenon, will itself diminish the hydrochloric acid of the gastric juice, since the regurgitated fluid is alkaline. Hurst has argued that the achlorhydria, however produced, may permit some infection to get past the stomach into the alimentary tract and cause the disease. This question can only be settled by finding out whether the achlorhydria, which is not an uncommon condition, always precedes the anæmia. At least one thoroughly substantiated case of pernicious anæmia is on record (Sophie Herzberg), where undoubted free hydrochloric acid was present in the gastric juice.

In conclusion, the three factors tending to produce the well-known achlorhydria of Addison's anæmia may be enumerated.

- (1) The anæmia.
- (2) A possible intoxication of the gastric mucous membrane, which also produces the anæmia.
- (3) Regurgitation from the duodenum.

## IX. THE GASTRIC MUCOUS MEMBRANE IN ADDISON'S ANÆMIA

By R. M. PASSEY, M.D.

DR. PASSEY showed a section of the fundus of the stomach from a case of Addison's anæmia, the material having been removed at operation.

The section showed (1) the presence of oxyntic cells, though perhaps in smaller numbers than in the normal subject; (2)

\* Sophie Herzberg: *Virchow's Archiv.*, cciv. 129, 1911.



evidence of inflammation, the openings of the secreting ducts being choked with leucocytes; (3) very little atrophy indeed.

The case was one of Addison's anæmia with the typical blood picture, with nucleated red corpuscles and a high colour-index. There was no free hydrochloric acid in the gastric juice one hour after a test-meal.

He also showed a section of the fundus of the stomach of a case of achylia without Addison's anæmia, the material having been obtained at an operation for chronic appendicitis.

Oxyntic cells were present in apparently normal numbers, but there were quite marked inflammatory changes in the mucous membrane. Free hydrochloric acid subsequently appeared in the patient's gastric contents.

Lastly, he showed sections of the stomach of two cases of Addison's anæmia, obtained post-mortem. From one, a woman aged 42, with four months' history, sections of the cardia, fundus and pyloric portion of the stomach were shown. No oxyntic cells were seen, and there was marked atrophy of the mucous membrane, this being most severe at the cardia and least at the pyloric end, even after due allowance had been made for post-mortem degeneration. No test-meal had been given. The blood picture was a typical one, with nucleated red cells, a red cell count of 800,000 per c.mm., hæmoglobin 15 per cent., and colour-index 0·94. There was no iron reaction in the liver or spleen.

Of the other case, a man aged 62, with three months' history, a section of the fundus was shown. Atrophy was not a very marked feature. Oxyntic cells were present. A very marked iron reaction was given by liver and spleen. After a water-gruel test-meal free hydrochloric acid had been present. Red cells numbered 1,083,333 per c.mm., hæmoglobin was 30 per cent., and the colour-index 1·3. No nucleated red cells were found in the one blood examination made. In neither of these two cases was inflammation a feature.

Spirochætes were looked for in the stomachs of the three cases of Addison's anæmia and in the liver and spleen of the last case, without any positive results. The stains used were Giemsa's and Dobell's modification of Levaditi's silver method.

## THE LATE RESULTS OF OPERATION IN CASES OF GASTRIC AND DUODENAL ULCER

By J. J. CONYBEARE, M.B., Medical Registrar, Guy's Hospital.

IN spite of the fact that operative treatment of gastric and duodenal ulcer has been practised for over twenty years, there is still considerable divergence of opinion as to the respective merits of surgical and medical treatment. The present investigation into the after-histories of operated cases was initiated mainly as an attempt to determine to what extent symptoms had been permanently relieved by operation. Needless to say similar investigations have been carried out by others, but the conclusions have varied widely. Thus May<sup>1</sup> in a series of cases published in 1910 finds about 60 per cent. of cures, whereas others find a percentage of cures up to 90 per cent. It must be remembered, however, that surgical statistics are often largely based on the results in cases operated on in the course of private practice, whereas the present inquiry, like that of May at the Middlesex Hospital, deals only with hospital patients. Naturally the latter class is far less likely to have satisfactory after-treatment, and is therefore less likely to give a high percentage of cures.

The present figures are based on the reports of one hundred and ninety patients operated on at Guy's Hospital between the years 1910 and 1915 inclusive, who left the hospital alive and relieved. No case has been taken into the series in which the notes did not specify clearly the condition found at operation and the nature of the operation performed. Otherwise, with the exception of perforated ulcers, all cases have been included, so that the series may be regarded as unselected. All the patients were ordinary hospital cases treated in the general wards.

The nature of the operative measures employed varied widely from the ordinary gastro-jejunostomy on the one hand to colectomy on the other. Naturally, however, gastro-jejunostomy was the operation performed far more frequently than any other. After gastro-jejunostomy simple excision of the ulcer is next in the number of cases, while all other operations

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were relatively infrequent. The number of times each operation was performed is shown in Table I.

TABLE I.

	No. of cases.	Percentage.
Gastro-jejunostomy . . . . .	150	79
Excision of ulcer . . . . .	13	7
Excision of ulcer and gastro-jejunostomy . . . . .	6	3
Other operations . . . . .	21	11

Other operations in Table I. include ileo-sigmoidostomy, colectomy, partial gastrectomy, gastroplasty, and invagination of ulcer, but the total number of times each of these operations was performed is so small that no deductions can be drawn as to their success or otherwise.

### *Operative Mortality*

No exact figures are available of the operative mortality, as the only cases accepted for the present series were those in which the clinical notes were sufficiently full to give exact information about the condition found at operation and the procedure adopted. Consequently there were many apparently successful cases of gastro-jejunostomy and other operations excluded from the series on the above grounds. The mortality in hospital among cases in which gastro-jejunostomy was performed, and in whom definite ulcers were proved to be present either at operation or autopsy, was 9 per cent. Probably, however, if all the other cases done during the years in question were added the mortality would not be found to exceed 5 per cent. When it is remembered that the operations were all done over seven years ago and are not the results of any one surgeon specialising in gastro-intestinal work, the mortality does not appear unduly high. Naturally in the case of more severe operations, such as colectomy and ileo-sigmoidostomy, the mortality figures are higher.

### *Age and Sex Incidence*

Although outside the original scope of the investigation, it may be interesting to compare the age and sex incidence in the present series with the findings in the long series of cases recorded by the Mayo Clinic.<sup>2</sup> In the case of gastric ulcers the average age in males at which operation was performed is 42 years, and in females 41. The corresponding figures for the Mayo Clinic are 47 and 44·7. In the case of duodenal ulcers the

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average age in this series in males is 43 years, which exactly corresponds with the figure given by the Mayo Clinic in a series of 814 cases.

As far as sex incidence is concerned duodenal ulcer occurred in females in four cases only out of forty-seven; *i. e.* over 90 per cent. of the duodenal ulcer cases were in males. The corresponding Mayo Clinic figure is 77 per cent. Among males, on the other hand, there is in this series no example of hour-glass contraction of the stomach. In three series of cases of hour-glass stomach, quoted by A. F. Hurst and R. P. Rowlands<sup>3</sup> out of one hundred cases, only fifteen occurred in males.

### *Localisation of the Ulcer*

The information in the case reports as to the exact site of the ulcer is not always very explicit. It is convenient to group them in three classes, (1) ulcers of the stomach, (2) duodenal ulcers, (3) pyloric ulcers. It is probable that few of those falling under the third heading really involved the pylorus itself, the majority being either duodenal or gastric ulcers extremely close to the pylorus. As, however, there is no means of classing them correctly, they have been grouped together as pyloric ulcers. Table II. gives the number of each class of ulcer found in the present series and also in fatal cases, on whom post-mortems were made after operation.

TABLE II.

	Total number.	Percentage of total cases.
Gastric Ulcer . . . . .	109	50.3
Duodenal Ulcer . . . . .	51	23.6
Gastric and Duodenal Ulcers . . . . .	4	1.9
Pyloric Ulcers . . . . .	52	24.2

If these figures are compared with those of the far larger series of cases recorded by the Mayo Clinic,<sup>4</sup> it will be seen that the proportion of duodenal ulcers in the present series is distinctly low. For the years 1910 to 1915 at the Mayo Clinic 70 per cent. of the cases were duodenal and only 30 per cent. gastric. Even if a proportion of the cases classed as pyloric in this series were really duodenal, it would still appear that the proportion of duodenal ulcers in the present series is distinctly low. A possible explanation of this fact may be that a larger proportion of duodenal than of gastric ulcers are treated at Guy's Hospital by medical means.

*System of Classification of After-histories*

To all patients in the series a letter was sent requesting them to fill up a printed form, consisting of a number of questions about their health after leaving hospital. In the cases where a reply was received an attempt was made to see the patient personally, though in many cases this did not prove to be practicable. In a proportion of cases who were seen at the hospital, x-ray examinations were made, and also in some cases a fractional test-meal was performed. The results of these examinations are discussed later.

The length of time that intervened between the operation and the receipt of information about the health of the patient varied from eleven years to two years. In 70 per cent. of the cases traced the operation had been performed over six years previously, and in only 2 per cent. of cases was the period of observation less than three years.

An attempt has been made to classify the patients from whom replies were received into four groups as follows—

Group A. Those with no digestive symptoms of any kind since their operation.

Group B. Those with slight abdominal symptoms, or who need to diet themselves, but who have no severe symptoms.

Group C. Those who are relieved to some extent, but who are still subject to recurrence of the symptoms for which they underwent operation.

Group D. Those whose symptoms have been but little if at all relieved, or in whom further operations were necessary.

In addition to the cases which fall into the above four groups a certain number of patients were ascertained to have died between the date of operation and the receipt of the inquiry into their condition. This was the case in twenty out of the 190 cases in the series or about 10 per cent. Taking into account the fact that the average age of the patients was over 40 years at the time of operation, the number of deaths subsequent to operation is probably but little higher than it would be among a group of the general population of similar age. Rather similar results were obtained by an investigation into the life expectancy of patients operated on for gastric and duodenal ulcer at the Mayo Clinic.<sup>5</sup>

Of the twenty persons ascertained to have died, in six cases death appeared to have been due to gastric disease, or at any rate with symptoms similar in kind to those for which the

patient underwent operation. In four out of the six cases death was undoubtedly due to gastric carcinoma. The period that elapsed between the operation in Guy's Hospital and death was in two cases two years, in one case a year and ten months, and in one case ten months. In all four cases gastro-jejunostomy had been performed without excision of the ulcer. Three of the above cases had less than a year's history of gastric symptoms before operation and may reasonably be regarded as cases of primary gastric carcinoma. The fourth had six years' history of pain, vomiting, and hæmatemesis, and was certainly a case of carcinoma supervening on a chronic ulcer.

One other case died with gastric symptoms suggestive of carcinoma four years after operation. The sixth case died in St. Thomas's Hospital with a gastro-colic fistula, six years after a gastro-jejunostomy.

Of the remaining fourteen cases ascertained to have died the cause of death was unknown in seven cases. In the remaining seven cases two cases died of pneumonia, and one case of each of the following diseases, phthisis, cerebral thrombosis, heart failure, general paralysis, and Addison's anæmia.

#### *The After-history of Traced Cases*

Of the 190 cases in the series, twenty patients, as stated above, were found to have died subsequent to operation. Of the remaining 170 cases 108, or 57 per cent., were traced. Although this percentage may appear low it must be remembered that twenty cases, or 10 per cent., were found to have died, this bringing the total percentage to 67 per cent. When the fact that the War intervened between the date of operation and the inquiry is taken into account the results do not seem so very unsatisfactory.

The 108 traced cases are distributed into Groups A, B, C, and D, as follows—

Group A.	41 cases	.	.	.	38 per cent.
Group B.	28 cases	.	.	.	26 per cent.
Group C.	23 cases	.	.	.	21 per cent.
Group D.	16 cases	.	.	.	15 per cent.

Naturally it has not been easy to assign each individual case to its correct category, especially in the cases where a personal interview was not possible. Every attempt has, however, been made to avoid any prejudice in the grouping.

Reviewing the figures as a whole, it would appear that some 65 per cent. may be regarded as cured, or at any rate very much

better after operation, while the remaining 35 per cent. either have had recurrences of their symptoms or are little, if at all, improved. These figures approximate very closely to the smaller series of patients who were followed up at the Middlesex Hospital by May. They do not, however, compare favourably with the results published by a number of individual surgeons. It must, however, be remembered that the present series includes none but hospital patients, who are probably more subject to recurrence of symptoms than private patients.

*Localisation of Ulcer and After-histories*

From the results of the present inquiry it would appear that the prognosis after operation is considerably more favourable in cases of duodenal and pyloric ulcers than in those of the body or the stomach. Table III. shows the groups, into which the cases fell according to their after-history, where gastro-jejunostomy was performed.

TABLE III.

	No. of cases.	Group A.	Group B.	Group C.	Group D.
Gastric Ulcer . . .	39	15	8	7	9
Duodenal Ulcer . . .	30	14	8	4	4
Pyloric Ulcer . . .	25	9	9	6	1

From the above figures it will be seen that only 59 per cent. of operated gastric ulcers fall into Groups A and B (completely cured or very much better), whereas 73 per cent. of the duodenal, and 72 per cent. of the pyloric ulcers come into these categories. Hence the prognosis after gastro-jejunostomy is apparently much better in duodenal ulcers or in those near the pylorus. In cases where pyloric stenosis was present the results of operation were even better, as over 80 per cent. of cases fall into Groups A and B. The type of case which tended to do badly with operation was the lesser curvature ulcer.

*Excision of Ulcers*

Excision of an ulcer without gastro-jejunostomy was performed in fifteen cases. In thirteen out of these the ulcer was on the lesser curvature, and in two cases on the posterior wall of the stomach. One case died in hospital some weeks after operation, and on post-mortem the mucous membrane was found to be ulcerated all round the site of the excision over an area of  $2\frac{1}{4}$  by  $1\frac{1}{4}$  inches. There had been much vomiting, and death apparently was due to exhaustion. Of the remaining fourteen

cases twelve were successfully traced. Of these only two had remained free from symptoms after operation. Two had only slight abdominal symptoms and fell into Group B. Of the remaining eight cases, six were classified Group D and two Group C. Although the total number of cases is small, the results appear very unsatisfactory as regards cure, as over two-thirds of the traced cases suffered from recurrences or were not improved by their operation.

Six cases in the series were treated by excision of the ulcer and gastro-jejunostomy. Unfortunately only three of these cases could be traced. Two were completely successful and the third suffers from slight abdominal symptoms.

#### *Causes of Recurrence of Symptoms after Gastro-jejunostomy*

In attempting to fathom the pathological processes which underlie the unsuccessful cases in the series we enter upon the most difficult part of the subject. It is naturally only in the patients who have actually been seen and examined that there can be any hope of reaching definite conclusions about the cause of persistence of symptoms. Even so, peptic ulcers are so notoriously subject to temporary relapses and remissions that the patients who came up to the hospital for examination often did so at periods when their symptoms had abated. Further, by no means all who were actually seen were willing to undergo investigations, such as test-meal or x-ray examination. It is therefore difficult, if not impossible, to say with any exactitude to what cause persistence of symptoms was due.

Of the cases in Group B, *i. e.* those complaining of slight abdominal discomfort but without severe symptoms, those who were investigated with a barium meal and the x-rays showed extreme rapidity of emptying of the stomach. On asking them to describe their symptoms they usually agreed that their main trouble was a feeling of distension immediately after taking food. This symptom has been described by Dr. A. F. Hurst,<sup>6</sup> who explains it as due to rapid distension of the coils of the jejunum owing to free passage of food from the stomach through a wide gastro-jejunostomy stoma. In some of the cases in this series we have been able to show both radiographically and by the fractional test-meal that the stomach empties with extreme rapidity. In several of the cases examined with the fractional meal it was found that, after taking one pint of gruel, the stomach was completely empty in sometimes as little as half an hour compared with the average normal time of emptying of two and a quarter hours. Several of the patients, who complained of the above symptoms, had already discovered for themselves



that they experienced considerable relief by lying down after meals for half an hour, especially by lying on their right side. This position presumably caused the food to gravitate towards the pyloric end of the stomach instead of leaving at once viâ the stoma. The symptoms can often be relieved by taking small meals at rather more frequent intervals than usual.

Of the patients who had serious recurrence of symptoms after operation, in comparatively few has it been possible to make any exact diagnosis. Many of them have had attacks of pain and vomiting, sometimes with hæmatemesis, which to the patient seemed exactly like those before operation. On the whole the pain tended to be less severe than it had been before operation. In cases which came under observation during a recurrence, it has sometimes been possible to demonstrate a tender point at x-ray examination, which corresponded to the site of the original ulcer. It may be presumed, therefore, that, in some of the cases at any rate, either the original ulcer has remained unhealed or there has been recurrence of ulceration at the same point.

On the other hand, recurrence of symptoms may be due to the development of a gastro-jejunal ulcer. In only five cases in the series was this condition demonstrated at operation, but it is highly probable that a proportion of the other unsuccessful cases may have had the same condition. In at least one case with a history of recurrence, no barium could be seen passing the stoma, and a fractional test-meal showed delayed emptying. At the time when the patient was seen he had no acute symptoms, but there can be little doubt that he had suffered from a gastro-jejunal ulcer, which had cicatrised, causing stenosis or obliteration of the stoma. Of the cases of duodenal ulcer several had suffered from recurrent attacks of melæna, causing a marked anæmia. These symptoms were probably due to the formation of a jejunal ulcer.

Many of the unsuccessful cases who came up to the hospital to be examined were found to be suffering from severe grades of pyorrhœa and dental caries. This, however, was also the case in many successful cases. It is probable that constant swallowing of pus from the gums may tend to prevent an ulcer healing or produce a new one. As a precaution the teeth of every patient should be carefully examined and removed where necessary some time before operation, and the patient instructed to have the teeth examined periodically after operation.

X-ray examination of the stomach was performed in twenty-seven cases. Ten of the patients so examined complained of no gastric symptoms of any kind, and in nine out of these ten

cases barium was seen to leave viâ the stoma only, and in one case only did it leave both by the stoma and through the pylorus. Of the remaining seventeen cases, in whom abdominal symptoms had occurred after operation, in ten barium was seen passing through the stoma only, in three cases it passed both viâ the pylorus and stoma, in three cases no barium was seen to leave the stomach during the first examination on the x-ray screen, and in one case it left by the pylorus only. In the majority of cases the barium left the stomach very rapidly through the stoma when the patient was examined in the erect position. In those patients who had both test-meals and x-ray examinations, it was found that, judging by the test-meal, those in whom the stoma was working well emptied in anything from half an hour to one and a half hours, compared with the average normal emptying time of two and a quarter hours. In several cases gastric delay as demonstrated by x-rays was confirmed by the fractional test-meal.

X-ray examination is apt to give a rather false impression about the rate of stomach emptying, especially if a fluid emulsion of barium is used. The weight and consistency of the meal allow it to fall almost of its own weight through the gastro-jejunosomy stoma, so that it sometimes almost appears as if it passed straight through the stomach into the jejunum. A meal of thicker consistency, such as porridge mixed with barium sulphate, should be used, which does not leave the stomach quite so rapidly. But even if all possible allowances are made for experimental error, there can be no doubt that after a gastro-jejunosomy the normal length of time during which food remains in the stomach is very much shortened. Further, it would appear that in many cases this does not apparently affect digestion, for many of the patients who showed very rapid emptying viâ the stoma appear to enjoy excellent health, or suffer from only slight symptoms. Of the cases examined radiographically, who presented no symptoms after operation, in only one was barium seen passing the pylorus and then only in small amounts. Occlusion of the pylorus was performed at operation in only very few cases, so that it would appear that when a gastro-jejunosomy is done, the food no longer passes through the pylorus, at any rate to any considerable extent. All the patients, in which no barium could be demonstrated to be passing through the gastro-jejunosomy stoma, had suffered from recurrence of symptoms at some time since operation. Those symptoms must presumably have been due to ulceration around the opening, which ultimately led to cicatrization and closure of the stoma.

*Fractional Test-meals in Cases of Gastro-jejunostomy*

Fractional test-meals were performed in twenty-eight cases of gastro-jejunostomy. The latter operation had been performed in some cases as long as eleven years before, and in no case was the interval less than six years. The oldest patient examined was 80 years of age, and the youngest 31, but the greater number of the patients examined were between 45 and 55.

Unfortunately it was only possible to carry out a test-meal with a small proportion of the patients who have been traced, as a good many, especially among those who had been perfectly well since operation, were unwilling to submit to the discomfort and loss of time involved.

Of the twenty-eight cases examined eighteen were among the patients in Groups A and B (*i. e.* those with no gastric symptoms of any kind, or with but slight symptoms). The emptying-time of the stomach in these cases, as judged by the absence of starch and sugar, varied from half an hour to two hours and a quarter, the average time being a few minutes over an hour. Of these eighteen successful cases, the acid curve showed no free hydrochloric acid and a low total acidity in ten cases, a hyperchlorhydria more or less marked in four cases, and a normal acid curve in three cases only. In one case, though free hydrochloric acid was not absent completely, it was below normal limits.

Of the four successful cases with hyperchlorhydria three had suffered from duodenal, and one from pyloric ulcer, possibly really duodenal. Of the three cases with a normal acid curve one was a duodenal ulcer and two pyloric ulcers. The hypochlorhydria case had been operated on for duodenal ulcer. Of the ten cases with no free hydrochloric acid, in one case the resting-juice only was examined, as the patient refused to wait. Of the nine remaining cases with achlorhydria only one was a duodenal ulcer, and he was a man of eighty years of age. The remainder were five of ulcer of the lesser curvature and three of pyloric ulcer.

An examination of these curves of patients, who have had but slight or no gastric symptoms after operation, tends to show that those who have had duodenal ulcers still have a high acid curve after gastro-jejunostomy, while most of those with gastric ulcers have a complete achylia, or at any rate a low or normal curve. Two examples of the fractional test-meal curves are given in Figs. 1 and 2. Thus it would appear that either complete achylia or most marked hyperchlorhydria after gastro-jejunos-

tomy is not inconsistent with perfect health and freedom from recurrence of symptoms of any kind.

Ten patients had test-meals performed, in whom the result of gastro-jejunostomy had been disappointing, the result being either recurrence of symptoms or but slight improvement. In these cases the stomach emptying-time varied from three-quarters of an hour to three hours, the average time being just

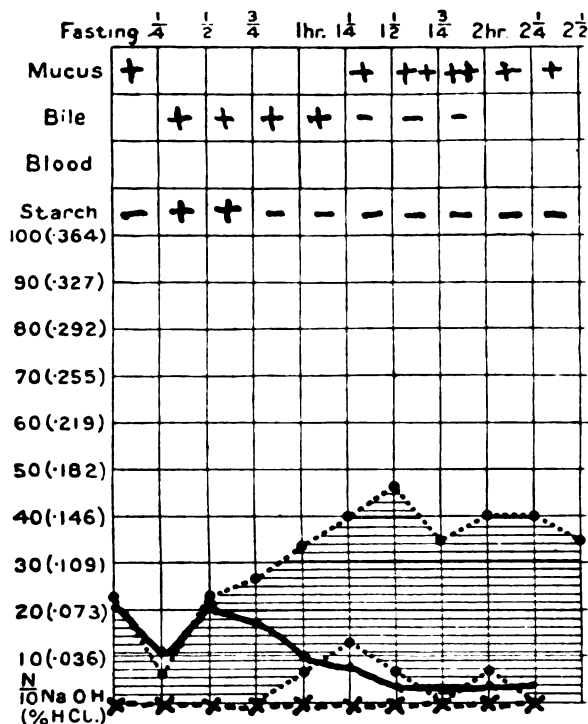


FIG. 1.

Ulcer of lesser curvature with gastro-jejunostomy done nine years previously. Age 52. The shaded area represents the limits of 80% of normal cases.

— = ACIDITY.

.... = FREE HCL.

over an hour and a quarter. As far as this point is concerned there is, therefore, no marked difference between the successful cases and the failures.

Of the unsuccessful cases three showed complete achlorhydria, two hypochlorhydria, three a normal acid curve, and two hyperchlorhydria. Here again the two cases with hyperchlorhydria had suffered from duodenal ulcer. Of the five with hydrochloric acid either completely absent or abnormally low, two were pyloric ulcers, two duodenal, and one lesser curvature.

Of the three normal acid curves one case was pyloric ulcer, one lesser curvature, and one duodenal. In the unsuccessful cases, therefore, there does not appear to be any constant type of test-meal curve. Recurrence of symptoms takes place quite as often with absent or low acid content as with hyperchlorhydria.

Unfortunately none of the patients, who had test-meals performed subsequent to gastro-jejunosomy, had had fractional

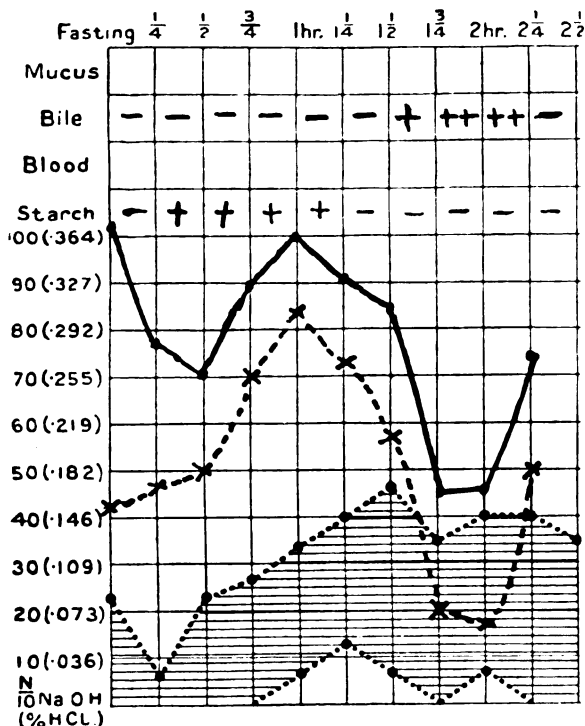


FIG. 2.

Duodenal ulcer with gastro-jejunosomy done nine years previously.  
Age 64. The shaded area represents the limits of 80% of normal cases.

— = ACIDITY.      .... = FREE HCL.

test-meals done before their operation, so that no comparison of curves before and after operation is possible. Some of them, however, had had the ordinary one-hour test-meal before operation. Although no real conclusions can be drawn from a comparison between the two test-meals, owing to the small number of cases in which results are available, it would appear that after gastro-jejunosomy the acidity is not markedly altered. The duodenal ulcers, who before operation have a high acid, may, even years after operation, present an acid curve

little if at all lower than before operation. Gastric ulcers, especially of the lesser curvature, often have a low acid before operation, and after operation there is frequently complete absence of free hydrochloric acid.

From the results of the twenty-eight test-meal examinations done in this series it does not seem to be possible to correlate the acid curve with freedom from symptoms or otherwise. In several cases those with very high acid after gastro-jejunostomy have been most successful results, whereas many of the patients who show a complete achlorhydria, or at any rate a very low acid, have suffered most severely from recurrences, with all the symptoms, such as pain and hæmatemesis, which they had before operation. The only point that does seem clear is that the duodenal ulcers have usually a high acid curve both before and after gastro-jejunostomy. This is in keeping with Dr. A. F. Hurst's<sup>7</sup> contention that the predisposing cause of duodenal ulcer is a hypertonic stomach with excessive acid secretion, and whatever operation is done the patient still has the same hypertonic type of stomach.

#### *Addison's Anæmia as a Sequel of Gastro-jejunostomy*

It is interesting to find that one patient in the series died of Addison's anæmia in Guy's Hospital eight years after gastro-jejunostomy for an ulcer of the lesser curvature. Unfortunately no test-meals were done in this case either before or after operation. It is remarkable, however, that the fractional test-meal curve in Addison's anæmia always shows complete achlorhydria with rather rapid emptying, exactly like that found so frequently after gastro-jejunostomy for ulcers of the lesser curvature. Whether achlorhydria resulting from the gastro-jejunostomy led to the development of pernicious anæmia is a matter for speculation.

#### *Conclusions*

1. Of the patients operated on for peptic ulcer and traced over periods from three to eleven years, about 60 per cent. are either completely cured or suffer from only slight abdominal symptoms. About 40 per cent. either died of gastric disease, suffered from recurrences of their symptoms, or were but little improved.

2. As regards results of different operations, simple resection of ulcer gave very unsatisfactory results. In only one-sixth of the cases was the result really good. With gastro-jejunostomy about 65 per cent. of the cases were found to be cured or much

improved, while 85 per cent. were unsatisfactory. The highest percentage of good results was obtained after gastro-jejunostomy in cases where there was pyloric obstruction. When the latter was not present, gastro-jejunostomy was slightly more successful in cases of duodenal ulcer than in those of gastric ulcer. Other operations, such as ileo-sigmoidostomy and colectomy, were done in too few cases to allow any opinion to be expressed as to results, except that these showed a rather high immediate mortality.

3. As regards test-meal results after gastro-jejunostomy there does not appear to be any definite type of curve. All that can be said is that most of the duodenal ulcer cases have a high acid after operation, while most of the lesser curvature ulcers show either a low acid or complete absence of free hydrochloric acid. There is no obvious correlation of symptoms with either high or low acid curves. Recurrences take place as frequently apparently in cases with no free acid as in those with a high acid.

4. X-ray examinations show that in nearly all cases very rapid emptying of the stomach takes place via the stoma, even ten years after the operation. Practically all the food leaves through the stoma and in only a few cases does it pass through the pylorus. If the stoma is found not to be working there is always evidence suggestive of gastro-jejunal ulceration having taken place at some previous date.

In conclusion, I wish to thank the physicians and surgeons at Guy's Hospital for allowing me to refer to the cases which have been under their charge in the hospital.

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## TWO CASES OF SYPHILIS OF THE STOMACH

By ARTHUR F. HURST, M.D., Physician to Guy's Hospital.

In a paper on Syphilis of the Stomach, read before the Royal Society of Medicine in November 1921, Dr. Gustave Monod<sup>1</sup> of Vichy gave a complete account of the French and German literature on the subject, from which it would appear that the condition is not uncommon. It is interesting to note, however, that Dr. Monod tells me that he has never actually seen a case himself. The American literature which he quoted gave a similar impression, although Carman and Miller<sup>2</sup> in 1917 only describe eight probable cases from the enormous material of the Mayo Clinic.

In contrast to that published abroad, the English literature on syphilis of the stomach is remarkably meagre. The impression gained from the discussion which followed Dr. Monod's paper was that the frequency of the disease has been much exaggerated on the Continent, and that most of the evidence brought forward in describing cases has been very inconclusive.

The only case in which a syphilitic lesion of the stomach has been demonstrated with complete certainty is the one shown and described at the meeting by Dr. J. W. McNee.<sup>3</sup> In this a large gummatous mass was found in the stomach post-mortem, death having resulted from perforation. The microscopical appearance was characteristic of syphilis, and innumerable spirochaetes were discovered in parts of the tumour. Dr. H. M. Turnbull<sup>4</sup> stated that among 13,000 post-mortems performed by him at the London Hospital he had only discovered one doubtful case of syphilis of the stomach, although in every abnormal condition of the stomach, in which there could be the slightest doubt as to its nature, careful examination had been made from this point of view.

It is obvious that no clinical case can be regarded as conclusive. I have been on the look-out for syphilis of the stomach for many years, and in a considerable number of cases in which the diagnosis seemed to be even remotely possible I have had the Wassermann reaction tested and other investigations carried out in order to determine whether the condition could be syphilitic in origin. In spite of this I have only had two cases in which the diagnosis seemed well founded, one a gumma simulating carcinoma and producing pyloric obstruction, and



the other apparently a syphilitic ulcer, clinically simulating an ordinary duodenal ulcer. There can be no doubt that the disease is extremely rare. None the less, from the remarkable effects of anti-syphilitic treatment in the two cases which I shall now describe, it is clear that in all anomalous cases of gastric disorder a Wassermann reaction should be tested, and perhaps it would be wiser to go still further and say that every case of probable ulcer or carcinoma of the stomach should be tested in this way.

*Syphilis of the Stomach simulating Duodenal Ulcer*

Mr. C. M., aged 51, has had digestive symptoms for twenty years, except from 1910 to 1915, when he was orange-farming in America and was completely free from symptoms. In all this period, especially during the last few years, the symptoms were very suggestive of duodenal ulcer, the pain coming on about three hours after meals, waking him up early in the night, and being relieved by taking food, though latterly the relief had been incomplete.

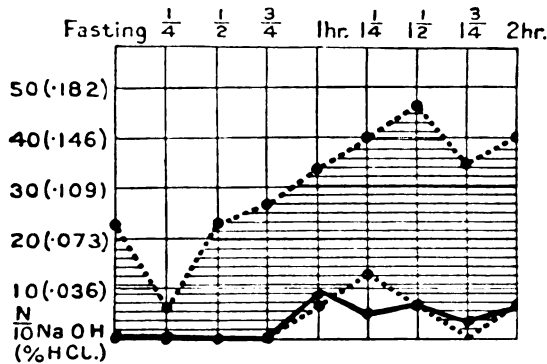


CHART I.—April 12, 1921. Before treatment.

Fractional Test-Meals in Syphilis of the Stomach. The shaded area represents the limits of free HCl in 80 per cent. of normal people. The continuous line represents the free HCl in this case.

Early in 1921 he was given a strict course of treatment for duodenal ulcer with rest in bed, diet and alkalies, lasting six weeks, but no improvement resulted. He was sent to me in April on account of his failure to respond to ordinary treatment. It was found that instead of the typical hyperchlorhydria and hypersecretion of duodenal ulcer he had marked hypochlorhydria (Chart I), and instead of the typical gastric hypertonus the stomach was atonic and dropped (Fig. 1), though it emptied itself after a barium meal within the normal limit of six hours. The gastric contents removed whilst fasting showed an enormous number of leucocytes. The stools constantly contained occult blood.

Although the patient had never had syphilis to his knowledge (though he had had gonorrhœa when twenty-one) the Wassermann reaction of his blood was strongly positive. A single injection of salvarsan, together with the administration of dilute hydrochloric acid and pepsin, resulted in such great improvement

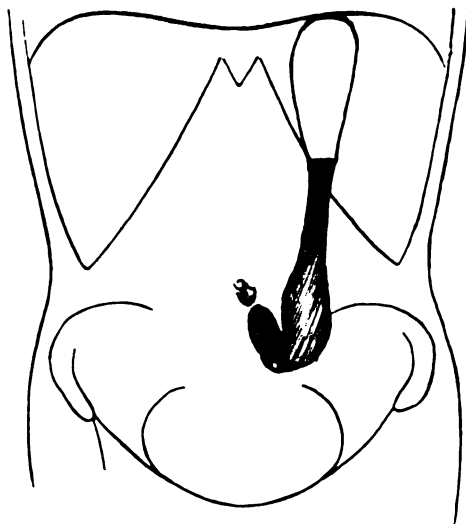


FIG. 1.

Dropped and slightly dilated stomach in erect position.

that he refused to have any more salvarsan until August, when the pain returned, but he continued to take the acid. He then had two more injections of salvarsan, since when he has been

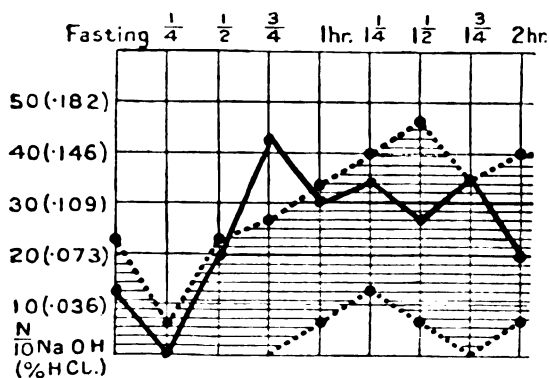


CHART II.—November 21, 1921. After treatment.

completely free from indigestion, although he has taken no hydrochloric acid since September.

His Wassermann reaction is still weakly positive, and he is therefore going to have another short course of salvarsan.

A fractional test-meal on November 21, seven months after he first came under observation, shows a slight degree of hyperchlorhydria (Chart II), in very striking contrast to the hypochlorhydria which was present at first. There is still a great excess of cells in the resting-juice.

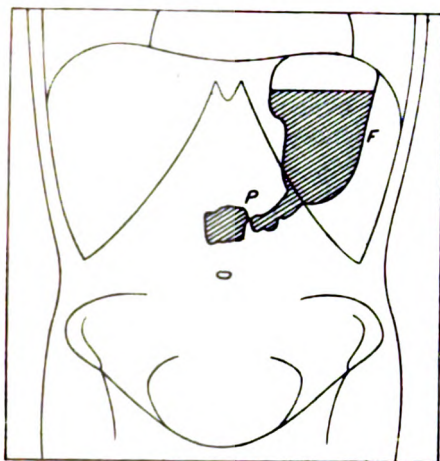


FIG. 2.

April 1912. (From skiagram by Dr. Ironside Bruce.)

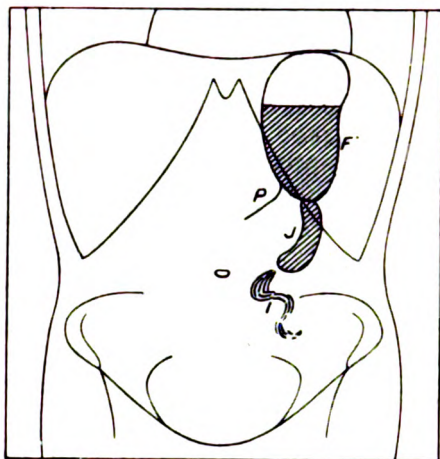


FIG. 3.

February 1913. After gastro-jejunostomy.

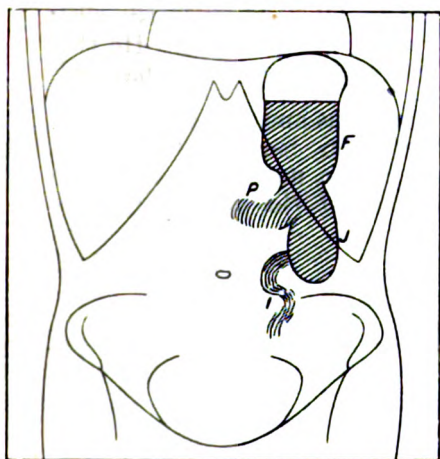


FIG. 4.

March 1915. Two years after salvarsan treatment. Standing.

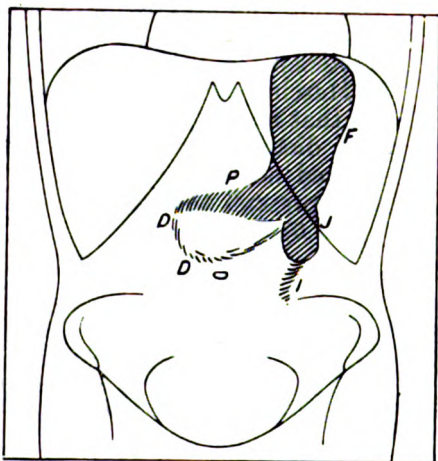


FIG. 5.

March 1915. Lying down, the patient having turned on his right side for two minutes.

Case II. Syphilis of the Stomach.—*F*, fundus; *P*, pyloric end of stomach; *D*, *D*, duodenum; *J*, jejunum, just beyond anastomosis; *I*, small intestine beyond *J*.

*Gumma of the Stomach causing Pyloric Obstruction*

Mr. G., aged 33, had syphilis in 1901. In 1909 he began to suffer from indigestion; his appendix, the lumen of which was partly obliterated, being removed in December. He was better for a time, but in June 1911 he complained of pain in the right hypochondrium, which was relieved by vomiting and by careful dieting, and of flatulence, wasting, and constipation, with slight tenderness beneath the right rectus. An x-ray examination is said to have shown that the stomach was normal, except that there was considerable delay in its evacuation, which was supposed to have been due to a duodeno-jejunal kink, and a diagnosis of intestinal stasis was made. In April 1912 Dr. Ironside Bruce found that the normal gastric outline was obliterated in the pyloric half of the stomach (Fig. 2). A gastro-enterostomy was performed in May 1912 by Mr. Peter Daniel. No ulcer was found, but the pylorus was rigid and the mucous membrane of the pyloric end of the stomach was hard and granular in appearance. There was only temporary improvement, and when I saw the patient with Mr. Daniel in February 1913 he was suffering from severe pain over the whole of the upper part of the abdomen, which was worst about four hours after meals and often awakened him at 2 a.m. The symptoms were similar to those he had before the operation, except that he did not now vomit. An x-ray examination (Fig. 3) showed that the food left the stomach very rapidly by the stoma, and the pyloric end of the stomach was completely obliterated. As it was thought that the condition might be due to syphilis, a Wassermann reaction was tried and found to be positive. Mr. Daniel therefore gave the patient three injections of neo-salvarsan. By April he was completely well, and when seen in March 1915, two years after the salvarsan injection, he told me that he had had no return of symptoms and was able to take full diet without any discomfort. An x-ray examination showed no great alteration, except that a narrow channel was now present through the pyloric end of the stomach (Figs. 4 and 5).

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## STUDIES ON TUMOUR FORMATION

By G. W. NICHOLSON, M.D., Lecturer in Morbid Histology, Guy's Hospital.

### II. TISSUE MALFORMATIONS. ANOMALIES OF BULK AND OF DIFFERENTIATION

BEFORE entering on the subject matter of the present study, it will be necessary briefly to review the theories which, in default of certain knowledge of the causation of tumours, have been advanced to explain them.

Tumours can be studied from the point of view of their ætiology or of their histogenesis. The ætiological theories attempt to furnish a complete explanation of the causation of neoplasms; those that are histogenetic aim merely at tracing them to the tissue cells in which they have arisen.

At least two kinds of factors come into play in the ætiology of every condition. These may be spoken of as the secondary or liberating causes, and the primary or exciting cause or causes. Thus, the melanomata of the skin always arise in pigmented nævi or moles, which are, as we shall see, malformations; the dermatitis set up by certain irritants is often the starting-point of an epithelioma; again, a high percentage of Fibiger's <sup>5</sup> rats, whose stomachs were infected with a nematode worm, developed gastric carcinomata. But not all moles end as melanomata, not every x-ray burn forms the starting-point of an epithelioma, and some of Fibiger's rats escaped a gastric carcinoma. Moles, irritants, and nematodes are therefore merely liberating causes, which enable some other cause to act and to reveal its activity in the shape of a malignant new growth. This cause (or these causes, as they well may be) is the primary or exciting cause of the formation of the tumour. Whether it be contained in the liberating causes or be something outside these we do not know.

If every mole were to form the starting-point of a melanoma, it would be the exciting cause of this form of new growth in the same sense as the tubercle bacillus is the exciting cause of a certain group of tissue reactions characterised by local proliferation of fixed cells, exudate of lymphocytes, and caseation, or as the action of a ray of light of a certain wave-length on the retina gives rise to a sensation of red. Beyond this point we cannot analyse primary causes. We do not know why rays of

light of a certain length appear red to us, whereas others that are shorter are violet, any more than we know why the tubercle bacillus does not produce gas gangrene. We know nothing of first principles.

A good deal has been written about individual susceptibility and predisposition to explain why one individual, after he has been exposed to an irritant, etc., develops a new growth, whereas another does not. But these expressions serve merely to cloak our ignorance in words.

The majority of the theories claim to explain both the ætiology and the histiogenesis of tumours. Three are of sufficient importance to be referred to here.

The parasitic theory maintains that a parasite, usually believed to be a protozoon or one of the blastomycetes, enters and multiplies within certain tissue cells, inducing them to proliferate and to give rise to a neoplasm. None of those that have been described have ever been shown to be more than contaminations. Others are now known to be ingested tissue cells. It has repeatedly been suggested that protozoa which resist all efforts to stain them are the causative agents. One must admit the possibility of the parasitic ætiology of some tumours. It is quite certain, however, that others, such as those with an organoid structure and the teratomata, are not the result of the action of a parasite, since, as has been pointed out by Schwalbe,<sup>21</sup> uniovular twins would then be caused by one.

The irritation theory is histiogenetic so long as it is used merely to compare the structure and behaviour of the cells in inflammatory and regenerative hyperplasias with those of new growths. When, however, it attempts to explain tumour formation as directly due to irritation, it becomes ætiological and fails signally. No explanation is given why growth is excessive and unlimited in one case, whereas it remains within physiological limits in another—limits that depend on the nature and intensity of the irritant, or the needs of the body for regeneration of the tissue, and on the capacity of the latter to regenerate.

The third theory was first formulated by Cohnheim,<sup>3</sup> whose name it bears, although its principles had been applied to isolated cases before him. Cohnheim's argument is as follows: Since every attempt to define a tumour fails, and as there are no distinctions and landmarks, either morphological or physiological, between inflammation and tumour formation, there must be some additional factor whereby the tumour-like neoplasm can be sharply distinguished from the inflammatory; and this can only be its ætiology. The irritation and infective theories fail, and one resource only appears to be left, namely,

the congenital disposition of the embryo. The real cause of a tumour is to be sought in a fault or irregularity of the embryonic rudiment of a tissue. This fault may consist of the production, at an early stage of development, of more cells than are required for the building up of the part concerned, so that there remain unappropriated a quantity of cells, which, owing to their embryonic character, are endowed with a marked capacity for proliferation. Tumours can therefore be defined as atypical new formations starting in an embryonic rudiment. They are progressive derangements of nutrition based on an inherent disposition, and are closely related to the monsters *per excessum*, and other malformations.

Cohnheim does not wish to insist too strongly on a superabundance of the cell material; it is perhaps more correct to speak of the material as having an abnormal inherent potentiality for subsequent tumour formation. The cells have received an abnormally strong vital impulse.

Towards the end of his paper he admits that every stratified epithelium has an inherent capacity for continued cell-production, and that its cells can penetrate into the connective tissue, when the power of resistance of the latter has been destroyed, even without the co-operation of a congenital epithelial germ or rudiment. Such conditions, of which he gives rodent ulcers and certain superficial canceroids of the skin, due to trauma, as instances, should be separated from true tumours and placed in a category of cancer-like indurations or ulcers, since there is not the slightest likelihood, to say nothing of necessity, that they should be referred to a congenital cause.

Surely, a theory that admits of such an argument is neither good science nor sound philosophy. As formulated by Cohnheim it is ætiological, since it attempts to explain the origin of all tumours in congenital malformations and abnormal predisposition of cells. That no cell of the body can, in any conceivable circumstances, produce a structure or perform a function to which it is not predisposed from the very moment of its origin is self-evident. But the question arises, and will have to be discussed, whether it is necessary to assume that the predisposition is, or indeed ever can be, abnormal.

Cohnheim's theory has been amplified and modified by many writers, among whom I will but mention Ribbert,<sup>18</sup> in whose hands it has been made to apply to cells that have become isolated by inflammatory and other pathological processes during the life of the individual, as well as to embryonic cell-rests. Ribbert has insisted that this separation is due to changes undergone by the connective tissue, resulting in dis-

turbances of tissue equilibrium; that the growth of every tumour is self-contained and independent of its surroundings; \* that it originates in one or more centres consisting of one cell or of a small group of cells which, by division and multiplication give rise to the whole of it; and that the neighbouring cells never become implicated in its growth. The elements of a neoplasm acquire no new biological properties, they proliferate because the normal resistance to their multiplication (tissue tension, ferment action, etc.) have been abolished.

The above, although not the first, is the form in which Ribbert's views are most generally known and accepted. He has, however, repeatedly modified them to an extent that renders them almost unrecognisable. Thus, in his last paper<sup>13</sup> on the subject, written a short time before his death, he comes to the conclusion that tumours in general and carcinomata in particular arise in developmental anomalies which, like all other germinal characters, are hereditary and have been inherent in the human race for all time. As they are recessive characters, they crop up only at intervals. Where, as in many carcinomata, irritation plays a part, the irritant merely stimulates the growth of a tumour "anlage." Where such an "anlage" is absent no new growth can develop.

Ribbert is not alone when he ascribes tumour formation to germinal anomalies. Several writers have maintained that it arises in cells that are abnormally predisposed from the very outset. This predisposition to neoplasia is to be regarded as a pathological germinal variation. It is quite unnecessary for these malformed cells to exhibit even the slightest anomalies of structure. The only means we possess of identifying them is by their behaviour, namely their neoplastic manner of growth, for whose induction no external stimuli are necessary. This mode of growth is therefore a character different and antithetic to every other. In Ribbert's own words, the cells have assumed a new biological property.

It will thus be seen that the embryonic theory assumes an inherent abnormal predisposition of cells, or their isolation or perversion during the course of their development, or, according to Ribbert's most popular modification (subsequently abandoned by him), as a result of inflammatory or allied changes. These cells remain *in situ* or are displaced, to come to rest at a distance from their place of origin. Their ultimate fate must be one of three: They die and are absorbed and cease to trouble us; or they undergo the fullest amount of differentiation their environ-

\* Cohnheim, starting from somewhat different premises, had reached the same conclusion.



ment permits, more or less synchronous with the rest of the body. The third possibility is that they remain dormant and in an undifferentiated condition for an indefinite time, at the end of which they are excited to proliferate by some injury or other stimulus. The relations of these undifferentiated cells to the tissues in which they are embedded have become grossly abnormal owing to the differentiation undergone by the latter. The growth of the dormant cells is, therefore, more or less autonomous. Because of this, and because they do not functionate, they are able to proliferate indefinitely and to give rise to a neoplasm.

It is impossible to estimate the merits of these theories and sub-theories without some knowledge of the evidence for and against them. All the points raised above will have to be discussed. I propose to begin with the tissue malformations or "embryonic rests" as they are popularly named. Characteristic examples will be given, and an estimate of their usual fate and consequent importance in tumour formation attempted.\*

#### TISSUE MALFORMATIONS

The sharp distinction that is usually drawn between malformations that have arisen *in utero* and those that have been acquired during the subsequent life of the individual is, in my opinion, a mistaken one. To begin with, gross development, as opposed to full differentiation, is by no means finished at birth. Again, it is usually implied, if not directly stated, that ante-natal differs from post-natal pathology in some mysterious way. This I very much doubt. Such a position is as absurd as the one that pathological processes differ from those that are physiological. An injury, be it mechanical or infective, or whatever be its nature, if it affects the embryo at an early stage of development, is bound to give rise to enormously more extensive and varied results than an identical injury when it takes place after the cells of the body have undergone differentiation and have therefore lost their early prospective potentialities.

A whole series of articles could be written on this fascinating aspect of congenital malformations, and I shall have to revert to it again. I will here describe a specimen which appears to me clearly to be the result of a slight lesion that had taken place in the early weeks of embryonic life.

At the post-mortem examination of a male adult the kidneys were found to be healthy, free from granular changes. A flat

\* Gross malformations will not be considered, since it is the small tissue anomalies alone that can be expected to throw light on the states of the cells that conduce to tumour formation.

linear accessory suprarenal, about 1 cm. in its longest diameter, was adherent to the anterior surface of one of them,\* at its upper pole. Fig. 11† represents a semi-diagrammatic view of a longitudinal section of this area, magnified five times. The strip of suprarenal consists of a double layer of cortex, folded upon itself, with a band of connective tissue and a large blood-vessel at the centre of its thickest part. The normal zones are present. For about two-thirds of its extent the accessory organ is firmly adherent to the surface of the kidney. Here the superficial part of the cortex of the latter contains a row of cysts, that varied much in size and were filled with the usual inspissated albuminous secretion. No cysts were found in any other part of either kidney. The renal capsule, not represented in the figure, passes uninterruptedly over the surface of the kidney and of the accessory organ, and is folded around the projecting end of the

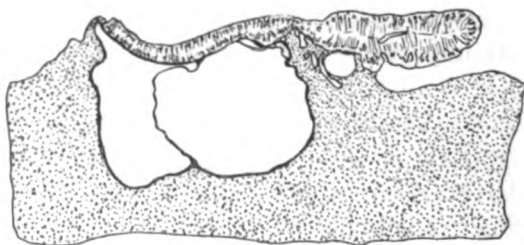


FIG. 11.

Strip of suprarenal cortex on kidney. Retention cysts beneath it. Magnif., 5

latter on to the surface of the kidney. It does not split to send a septum between them. The cysts are surrounded by a narrow zone of atrophied and fibrotic renal tissue, which rapidly passes into the healthy parenchyma of the organ.

I explain this anomaly by assuming that the apposed surfaces of the kidney and suprarenal became abnormally adherent to each other at some period of development prior to the third month, when the renal capsule is formed. During the subsequent differentiation and separation of the organs, these cells of the suprarenal were torn away from the rest of the gland, but were able to undergo a differentiation which is perfect, except for the anomaly of position. The presence of the renal cysts immediately beneath them and nowhere else in the kidneys can only be explained on the assumption that they

\* I cannot remember which kidney this observation refers to without the post-mortem record, which is not available at the moment.

† For convenience of reference the figures in this series will be numbered consecutively. A Roman numeral after the number of a figure denotes that of the article in which it appeared.

were caused by some inflammatory focus, that led to the occlusion of tubules and to retention of their secretion. If this lesion took place at an early period, when the suprarenal consisted of a small number of cells whose power of growth was still great, it will have been exceedingly minute, of so small a size in fact that, had it not occurred until after the active period of growth, its effects, and therefore its presence, would be quite unappreciable.

I have described this specimen out of its proper place, since its structure throws an unusual light on its causation, and suggests that some of the malformations of the embryo, at any rate, are the result of everyday pathological processes.

Gross malformations are common enough. It is certain that small tissue malformations are even more common. There are few people, for instance, who do not possess a cutaneous mole or two. The argument applies with equal force to the internal organs, but here malformations are not easily discovered and are often found only by accident. It was not until recently that the amount of attention began to be paid to them that they deserve; and our knowledge of them is still very imperfect. R. Meyer may be called the pioneer in this field. In 1905<sup>15</sup> he published a paper on the tissue malformations of the female generative organs, followed in 1911<sup>16</sup> by one on those of the same system in the male. In 1912<sup>17</sup> he described 300 cases from all parts of the body, mostly in embryos and infants. Among these, however, he included a few tumours whose origin he traced to malformations. Lubarsch<sup>11</sup> has made an important contribution to the subject in a paper read to the International Congress of Medicine in 1910. Three years later Herxheimer<sup>10</sup> collected our knowledge in the form of a text-book. I have for some years taken a considerable interest in these conditions, which are on the borderland of normal and morbid histology, and have collected a number. In describing these I shall omit, as far as possible, all the instances that show an excessive or blastomatous amount of growth, as they must be included among the hamartomata. It must be confessed, however, that it is often difficult, if not impossible, to draw the line between them.

Tissue malformations can be divided into anomalies of bulk, of differentiation, and of position and blending of one kind of cell with another.

The anomalies of bulk and of differentiation often proceed hand in hand, and it will be convenient to consider them together. If they are below the normal they are spoken of as *hypoplasias*,

if in excess as *hyperplasias*. In the case of differentiation the anomaly can also be one of direction; cells differing in structure from those characteristic of the part of the body are produced. Here we have a *heteroplasia* or *heteromorphosis*.

It must be remembered, however, that a hypoplasia is able to develop on the basis of a hyperplasia, and vice versa. Thus, the persistence of an embryonic structure which normally disappears again is an instance of a hyperplasia. But it often persists in a rudimentary, *i. e.* hypoplastic, form; *e. g.* the Wolffian body and duct in the female. I shall treat of these persistent embryonic organs under a separate heading.

The anomalies of position, and of blending of cells of different kinds to form tissues, and of tissues to produce organs can be subdivided according to whether they remain at the site of their origin, when they are said to be *dislocated*, or are removed from it during subsequent development to come to rest in an abnormal situation, in which case they are *emigrant*. Faulty blending may be due primarily to a hyperplasia of one tissue, or to a hypoplasia of another. If the epithelium is the part responsible, we can speak with Herxheimer<sup>10</sup> of an *active* dislocation or emigration. If the less highly organised mesenchyme is at fault, the process is said to be passive.

1. *The Hypoplasias*.—The well-known and often-quoted paper of Schaper and Cohen<sup>20</sup> must once more be referred to here. They pointed out that all the differentiated tissues that have not lost the power to regenerate contain physiologically hypoplastic cells. Proliferation and functional differentiation are antagonistic. Once a cell has reached a certain stage of differentiation it can no longer divide. They use the epithelia as examples, and show that, in squamous epithelium, it is in the elongated basal cells of the rete Malpighii alone that mitoses are found. In columnar epithelia and in secreting glands mitotic figures are limited to definite areas which correspond with the small efferent ducts into which the secreting acini open. These areas they name "indifferent zones," since they give rise to the secreting epithelium on one side, and to that of the larger ducts on the other. They are the germinal and regeneration centres.

It must not be supposed, however, that these indifferent zones are quite undifferentiated. Schridde<sup>22</sup> has shown, for instance, that the basal cells of the epithelium of the foetal œsophagus possess traces of the fibrillation characteristic of squamous epithelium.

The important point must be remembered that these zones perform a vital function by remaining hypoplastic in comparison with the other cells of the tissue. It is doubtful if the latter

could ever have attained to their high degree of differentiation and to their perfection of function except for their presence, unless the secreting glands were to have been built up on a totally different plan.

The kidneys of infants frequently present certain anomalies, which were first described by Herxheimer.<sup>9</sup> Fig. 12 represents a section from a healthy kidney of a female child of seven weeks. The epithelial cells covering the glomeruli are mostly round or oval. This is the normal appearance at this age, and shows that differentiation is not completed. Two glomeruli are very small and solid. A malformed one, with an irregular mass of nuclei projecting into a triangular Bowman's capsule, is to be seen about

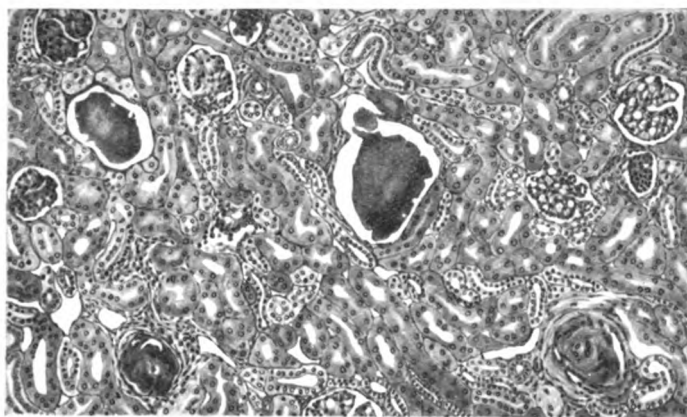


FIG. 12.

Arrests of development of kidney of infant. Magnif., 110.

midway between the lower ends of the two large cysts. Two hyaline glomeruli are also shown. The cysts are occupied by inspissated urine and retain traces of a flattened epithelial lining. Nowhere is there evidence of inflammatory change.

The small and malformed glomeruli are obviously arrested in their development. The hyaline changes are secondary, and are of universal occurrence in damaged glomeruli. It is now generally admitted that the glomeruli and secreting tubules of the kidney are developed from the epithelium of the Wolffian ridge, and the collecting tubules from the upper end of the ureteric bud of the Wolffian duct. If these structures fail to unite, the former become distended by the accumulation of urine, and cysts like those in the drawing result. Here again we have an arrest of development. Its cause is obscure, but depends on the highly complicated developmental history of the kidney.

These arrests of development are hypoplasias. Their chief interest to us depends on their fate. Two glomeruli in Fig. 12 had undergone hyaline degeneration; it is probable that their malformed fellows would have done so later. At all events, Herxheimer<sup>9</sup> is emphatic that they become less numerous as age advances and disappear entirely towards the end of the first year. The evidence, therefore, shows that they do not possess the slightest tendency to proliferate; they are all of them absorbed. The greater part of the epithelium of the cysts has disappeared; its remnants are flattened. Their only importance lies in the fact that they represent a very slight form of congenital cystic kidney.

There is another form of hypoplasia of the kidney which is said to be common in calves, but very few instances of which have been recorded in man. As it appears to be closely related to the common "embryonic" tumours of children, I must refer to E. Meyer's<sup>13</sup> case. In a girl of nine weeks, with several other malformations, the kidneys were of the usual shape and size, but contained numerous triangular slightly raised pale areas that extended from the surface to the pelvis. In microscopic sections they were seen to pass gradually into the healthy renal substance, and to consist of well-developed small glomeruli and of blindly ending straight tubules. The convoluted tubules were absent, but were represented by masses of cells that, in shape and size and occasionally in their grouping, corresponded with them. He points out that the glomeruli and straight tubules appear during the second month of embryonic life, and the convoluted tubules not until much later, and concludes that these areas are local arrests of development and differentiation.

Similar arrests of development are occasionally found in the liver, to cystic disease of which organ they bear the same relation that the small renal malformations bear to cystic kidneys. Fig. 13 represents the greater part of one of these. It was found accidentally in the sections in the immediate neighbourhood of a cavernous angioma of an otherwise healthy liver. It consists of fibrous tissue with hyaline changes and of numerous dilated bile channels, lined by a single layer of epithelium. In the lower right-hand corner of the drawing it is connected with the remains of a portal canal, in which a small healthy bile-duct is to be seen. v. Meyenburg<sup>12</sup> has studied these areas by means of serial sections. He concludes that the cystic channels are small bile-ducts which are always connected with liver cells, but end blindly below, where they never form a junction with the larger bile-ducts. He discusses their importance in the developmental history of the liver, and

draws attention to the old view that this organ has a dual development, like the kidney. The large bile-ducts are outgrowths of the hepatic diverticulum of the gut, and the liver cells and small bile-ducts arise in a solid mass of cells (? meso-blast) that forms a cap to them. It seems to me that there is a good deal to be said in favour of this view. It is the only one that explains the cases of congenital cystic disease of the liver.

Since angiomas are typical hamartomata, a class of borderline cases between malformations and tumours (*vide* p. 245 of the first of these studies), the association of the arrest of develop-

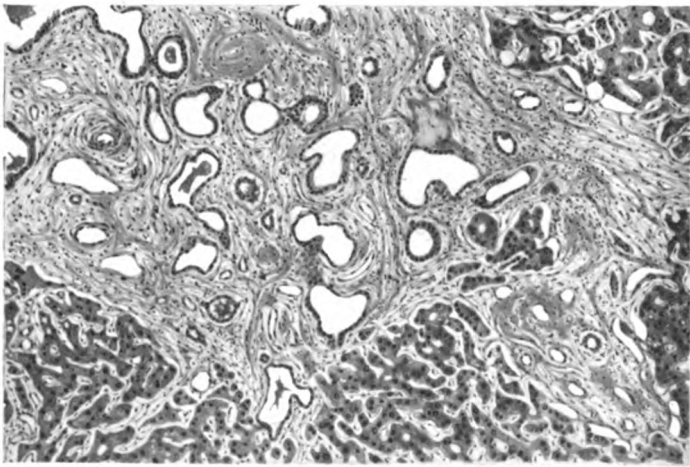


FIG. 13.

Arrest of development of liver. Magnif., 90.

ment in Fig. 13 with a cavernous angioma throws some light on the manner in which the latter has been formed.

Branchial cysts are perhaps the best examples of arrests of development (Fig. 14). They are usually lined by a mucous membrane of non-keratinised squamous epithelium, closely resembling that of the pharynx; or, much less frequently by a stratified columnar "respiratory" epithelium, whose cells, when well preserved, can usually be shown to be ciliated. In some specimens the two alternate (Fig. 14). Mucous glands are rarely found under the columnar epithelium. A typical feature of these branchial cysts is the presence of a large amount of sub-epithelial lymphoid tissue, in which nodes with germinal centres are often numerous. In one of my specimens there is a well-developed lymph gland within the capsule of the

cyst. In another the squamous epithelium has sent multiple crypts into the lymphoid tissue, so that a typical tonsil has resulted. The connective tissue of the wall is dense and fibrous or loose and areolar. In one case I have seen numerous small islands of fibro-cartilage, without a perichondrium. I shall revert to these later. Bundles of striated muscle and lobules of fat are occasionally present. I have, however, always been able to trace them to the neighbouring muscles and subcutaneous fat in the instances in which I have observed them, and do not regard them as essential primary constituents of the malformation.

The epithelium of the cysts is a derivative of the entoderm.

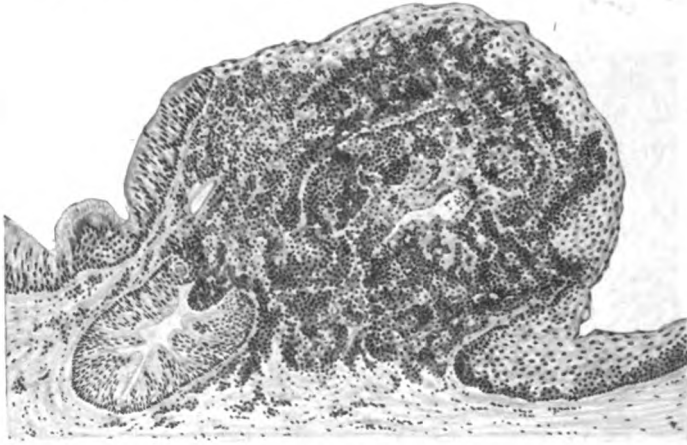


FIG. 14.

Branchial cyst. Pharyngeal and respiratory epithelium and lymph-node.  
Magnif., 80.

They originate in the branchial pouches of the pharynx. They are generally believed to be formed by the abnormal persistence and isolation of a superfluous part of one of these pouches, which fails to involute. But I know of no evidence that the whole of the epithelium of the pouches is not used in the development of the lateral lobes of the thyroid, the parathyroids, and the thymus, as well as the other tissues to which they give rise. A better explanation that does not postulate an excess of tissue has been advanced by Meyer.<sup>17</sup> Some of the cells of a pouch, which normally undergo differentiation into higher secreting tissues, have failed to do so, and have succeeded merely in producing simple forms of entodermal epithelium, those that line the pharynx and the respiratory tract, together with the mucous glands of the latter. (If the lymphocytes or corpuscles of the thymus are entodermal, then it is possible,



although perhaps unprovable, that those of the lymphoid tissue which is always present in branchial cysts may have the same history.) The anomaly is due primarily to a hypoplasia, or arrest of development. If we neglect for the moment the presence of cartilage, several explanations of which are possible, and explain the connective tissue wall as an instance of capsule formation, it becomes unnecessary to postulate more than an anomaly of the entoderm alone.

Among my specimens there is one composed of two independently encapsulated cysts, separated from each other by dense fibrous tissue and fat. One of these has the structure of a tonsil, its capsule contains a minute lobule of a salivary gland.

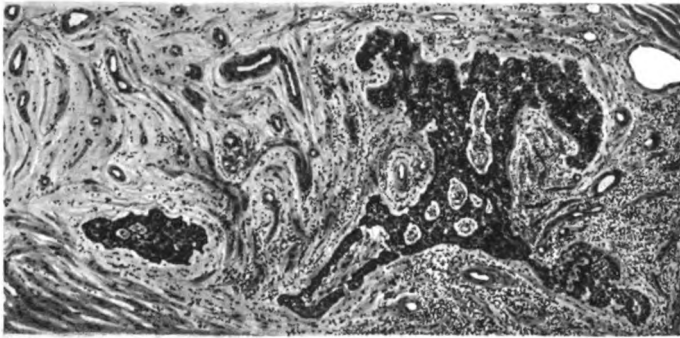


FIG. 15.

Suppurated branchial cyst. Inflammatory hyperplasia of epithelium.  
Magnif., 90.

The other is lined by freely keratinised squamous epithelium, with small sebaceous glands, aborted hair follicles, and one sweat gland. It here becomes necessary to assume an anomaly of the ectoderm of the branchial cleft in addition to that of the entoderm.

It remains for us to examine the degree of maturity of the epithelial constituents of branchial cysts. In those that I have seen they were always perfectly mature, and recognisable at once as pharyngeal and respiratory epithelium. Not once do they show signs of immaturity or the slightest tendency to proliferate to an undue extent. But these cysts are liable to become inflamed, and to suppurate. In one such specimen the squamous epithelium which has become macerated and desquamated in many places possesses a definite stratum corneum in others. It has grown down into the inflammatory granulation tissue (Fig. 15) as irregular branched papillæ,

many of which appear to be isolated in sections. They consist entirely of cells of the rete Malpighii, and are obviously in an active state of proliferation. *But these changes are purely secondary* and results of inflammation. They are strictly comparable, the one with the hyperkeratosis of the buccal and pharyngeal epithelium found in inflammatory conditions, and the other with the epithelial down-growths to be seen in almost every ulcer and mass of granulation tissue that have been formed on a surface covered by squamous epithelium. To use Cohnheim's<sup>3</sup> (p. 804) words: "For on reflecting that every stratified epithelium has an inherent capacity for continued cell-production, and that this productive power is augmented by hyperæmia, it will at once be apparent that, even *without the co-operation of an epithelial germ*, the cells of an epithelium may penetrate into the connective tissue, when the resisting power of the latter is destroyed."

I could not resist quoting Cohnheim, since the changes he describes have, in the present instance, been brought about in the manner in which he explains them, as a result of the hyperæmia of suppuration, in a developmental anomaly which he himself uses as an argument in favour of his theory (p. 772, "Subcutaneous dermoids of the neck"). They result from the action of an external stimulus or change of environment. That they have occurred in a branchial cyst is an accident.

Another anomaly due primarily to a hypoplasia is the so-called lingual struma, regularly found in cases of sporadic cretinism. This disease is characterised by complete absence of the normal thyroid, always associated with a tumour of the base of the tongue, which communicates with the foramen cœcum. Erdheim,<sup>4</sup> who was the first to describe it, states that it varies greatly in structure, and contains squamous and columnar ciliated epithelium, mucous glands, and aborted thyroid tissue. All these structures are derivatives of the thyroglossal duct, since they are found in its remnants when they persist. The duct arises as a bud of the pharyngeal entoderm at the foramen cœcum, and grows caudad; its distal end undergoes differentiation into the median lobe of the thyroid. Lingual strumas are therefore instances of arrests of development of the duct, which has failed to grow beyond its site of origin and has undergone a rudimentary form of differentiation into the simple lining epithelia and mucous glands of the entoderm. At best it produces only a few aborted thyroid vesicles. (It is of interest to note that, in the cases of sporadic cretinism examined by Erdheim, the lateral lobes of the thyroid, deriv-

atives of the fourth entodermal branchial pouches, were absent as well, and that the thymus was small. Schilder,<sup>21</sup> however, found a small nodule of thyroid tissue close to the upper parathyroids in a case of almost complete aplasia of that gland with cretinism, and regards it as the representative of its lateral lobe.)

An excellent instance of a hypoplasia is Healey's<sup>7</sup> case of ciliated epithelium in the œsophagus of a seventh-month foetus. It occurred as well-defined irregular patches, the stratified epithelium being pitted to receive them. Healey examined several early human embryos, the oldest of which was 16 mm. in length, but found no traces of ciliated epithelium in them. He rejects the possibility of a graft from the trachea, and concludes by stating that it remains to be demonstrated that at an early stage in its development the œsophagus is a ciliated tube. Had he examined older foetuses, or consulted Schridde's<sup>22</sup> monograph, he would have found that in those of from 44 to 110 mm., the greater part of the œsophagus is lined by ciliated epithelium, which later becomes desquamated. Traces of it are, however, occasionally found at birth. Healey's case is an arrest of development; the normal desquamation of the ciliated epithelium has been retarded in an unusual degree.

The hyaline glomeruli of the kidneys of infants, the branchial cysts and lingual strumas are typical examples of malformations that have resulted primarily from arrests of development or hypoplasia. The fact about them which chiefly interests us here is that their tissues are always mature. They have progressed in differentiation far beyond the point reached by the cells at the time at which they were formed.

It is not easy to fix the latest date at which our renal anomalies can have been produced, since the kidneys are not fully developed until after birth. A terminal period can, on the other hand, be easily fixed for branchial cysts and lingual strumas. Broman<sup>1</sup> (p. 286), states that the "anlage" of the thyro-glossal duct can be distinguished in embryos of 2.5 mm. (middle of third week). It soon elongates and its proximal end has usually atrophied more or less completely in embryos of 7-8 mm. (fourth week). According to Grosser<sup>6</sup> (p. 446), the pharyngeal pouches, as such, disappear at an early stage. The third pouch, for instance, is usually no longer extant in embryos of 14 mm. (sixth week). The oldest specimen in which its remains were present measured 24.4 mm. (seventh week). Whereas the kidney malformations have a late date of origin, which possibly extends into extra-uterine life, the others originate during the early weeks of development.

At these early ages the tissues of the embryo present a very undifferentiated or "embryonic" appearance, and since branchial cysts, etc., when we see them, have always a differentiated "adult" structure, it follows that in such cases we do not see the actual original hypoplasia, but the differentiated cells into which it has developed. This is an important point, and one I desire to emphasise. The cells of hypoplasias regularly undergo differentiation more or less simultaneously with that of the normal tissues. They are adult, well-differentiated cells, without signs of proliferation in excess of that found in normal structures, although Fig. 15 demonstrates that they participate in the infirmities of the flesh, that they react to irritants in precisely the same manner as do these.

I have drawn this conclusion here, instead of at a later stage of this study, since hypoplasias, because of their nature, should be the most "hypoplastic" of all tissue malformations.

But Cohnheim's theory postulates the common occurrence of cells that have remained undifferentiated or, at most, have attained to but a very slight degree of differentiation. It thus becomes imperative to look for them. They are usually spoken of as "cell-rests"; I propose to limit this term to them.

These cell-rests are always classified with the hyperplasias, since it is assumed that they consist of cells which were produced in excess at the first "anlage" of the tissue. They were therefore not used in its growth and development, and have remained in an undifferentiated condition. This is, in my opinion, a pure assumption, since there is not a particle of evidence in support of it. We do not really know what are the influences that regulate the size of organs, or to what extent the cells can proliferate when unchecked. Pathology teaches us that the amount of growth cells are capable of is far in excess of that necessary to produce the normal organs. What are congenital aplasias, hypo- and hyper-plasias due to? To irregularities in the size of the "anlage," or to secondary causes inhibiting or stimulating its growth? Again, and here we come to the object of this study, can such "rest" cells survive, since they perform no physiological functions? Until this point is settled, I prefer to regard cell-rests simply from their anatomical aspect, as groups of hypoplastic cells.

Since, with one possible exception, I have never seen a cell-rest, I must turn to the literature for information. I admit the possibility of my having overlooked an isolated record, in spite of having kept a sharp look-out. The truly remarkable fact confronts us that the published cases can be counted on

the fingers of both hands. E. Meyer's<sup>14</sup> malformation of the kidneys of an infant of nine weeks has been mentioned above. The convoluted tubules were represented by solid masses of cells, which were, however, sufficiently differentiated to be easily recognisable. Hedren<sup>8</sup> saw very similar areas around an "embryonic" tumour of the kidney of a child of eight months. Schridde<sup>22</sup> figures a non-fibrillated epithelial cell among the fibrillated squamous basal cells of the foetal oesophagus. He<sup>23</sup> found identical cells in the lips of foetuses of the last two months of pregnancy. Lubarsch<sup>11</sup> has observed undifferentiated cells in the suprarenals, kidneys, and livers of infants, especially of those suffering from congenital syphilis. R. Meyer<sup>17</sup> has a record of the presence of undifferentiated epithelium in the cervix, another in the vagina, and a third of a heap of granulosa cells in the cortex of the ovary. All these were found in full-term foetuses. The only observation of the kind I have made is more than doubtful. I found a small collection of round basophile cells in the medulla of a suprarenal of a young woman. But I cannot exclude their being lymphocytes, although there is no evidence of inflammation around them. I mention them merely to point out how difficult it is to identify these cells.

The fact, however, remains that they have been identified on several occasions by pathologists who have systematically looked for them. In the case of squamous epithelium, at any rate, whose cells are fibrillated, the task of finding them should not be an impossible one. In every single indisputable case they were present in the foetus or in very young children. This fact has been commented on by all the writers on the subject. They all come to the conclusion, which is, as a matter of fact, the only rational one, that cell-rests always die and are absorbed, unless they complete their differentiation, since they have never been demonstrated in older children or in adults.\*

\* While these pages were in the press, I have had occasion to read some of the literature on tuberous sclerosis of the brain. This disease is characterised by the presence of areas of localised gliosis of the grey matter, in which the normal arrangement and grouping of the ganglion cells is disordered. Many of these cells are large, pale, and often multi-nucleated. These areas are arrests of development, and present the characters of the hamartomata of Albrecht. Tumours, which are generally multiple, are found in other organs, such as the skin, heart, thyroid, intestines, and the kidneys. I must here draw attention to Fischer's (*Ziegler's Beitrage*, L. p. 235, 1911) paper on the latter. In a young individual he found areas in which the glomeruli are immature and solid, and without capillaries. The tubules are absent; their place is taken by solid bands of epithelial cells. It cannot be denied that these areas are arrests of development. They correspond very closely with the case of Meyer referred to above. Those described and figured by Fischer occurred in a boy of three. In later life they are replaced by nodules of adipose tissue, plain muscle, and thick-walled arteries. It appears, therefore, that the life of these arrests

I must here express a doubt if it is ever possible for undifferentiated cells that perform no function to survive. If Schridde's <sup>22</sup> cell of the œsophagus, for instance, which, as far as I can see, must have been subjected to an environment identical with that of the fibrillated cells surrounding it, was unable to complete its differentiation, there must have been something wrong with it. I cannot understand why, in that case, the body should have failed to treat it like every other diseased cell. If it succeeded in resisting its efforts to remove it, it would at a later period have become encapsulated and thereby rendered easily visible. But there are no records of such encapsulated undifferentiated cells in adults. Again, take the case of branchial cysts. There must be some reason why the body, which is able to deal successfully with much larger inflammatory lesions, fails to absorb these useless embryonic remains. It is, surely, because they are built up of mature cells, strictly comparable with those that line the pharynx and the trachea. I believe that we should distinguish between two kinds of cellular activity, the physiological, which is of use to the body, and the histological or tissue function, which need be of no use except to the cell itself. In order to justify their existence and to escape destruction cells must perform the latter, even though it be nothing better than to form a lining to an adventitious cyst. But they cannot perform this function if they remain undifferentiated. The "immature" ova and the spermatogonia are no exceptions to this. I believe that Child <sup>2</sup> is perfectly correct when he claims that they are old, mature cells. Nor do Schaper and Cohen's <sup>23</sup> indifferent zones vitiate the argument, since by remaining more or less undifferentiated they perform a function which is indispensable to the continued existence of the tissue.

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of development is limited, and that they do not persist indefinitely in the undifferentiated state.

The most important point, however, of Fischer's observations is this. In a male of sixteen he found a small round solid heap of epithelial cells, connected with the side of a convoluted tubule, and a similar nodule with a collecting tubule in its midst. In a male of eighteen he observed small nodules of undifferentiated epithelium among the adipose tissue and the smooth muscle of the tumours. In a female of twenty-five a few small groups of epithelial cells without glandular arrangement were seen in the tumours. Fischer points out that these epithelial formations correspond exactly with the undifferentiated renal blastema. Unfortunately he does not figure them, and the explanation is possible that they were produced by secondary proliferation of the epithelium of renal tubules. To judge, however, from the general excellence of his paper, and the clearness of his descriptions, there is no reason to suppose that he was mistaken. Even if we leave out of consideration the last two of his cases, in which the epithelium formed part of definite tumours, the first case remains. Here these structures were found in the midst of the renal parenchyma. We cannot, therefore, get away from the fact that pieces of undifferentiated renal blastema, or true "cell-rests" in the sense of Cohnheim, do occasionally persist for sixteen years.

2. *The Hyperplasias*.—Pure hyperplasias that arise during the course of development are, from our point of view, chiefly of theoretical interest. As I have just said, they are assumed to be the nucleus on which embryonic cell-rests are built. They may also give rise to many of the errors of blending.

Practically every suprarenal contains microscopic areas of hyperplasia of the cells of its cortex. They are as common in children as in adults. The only foetal suprarenal I possess happens to contain them.

Fig. 16 represents a general enlargement of the thyroid, said to have been present since birth in a child of three. It shows complete absence of colloid and a hyperplastic and proliferative form of degeneration of its epithelium, and is indistinguishable histologically from many a well-established case



FIG. 16.

Congenital enlargement of thyroid. Magnif., 170.

of Graves' disease. It appears to me to be an excellent example of the truth that ante-natal does not differ from post-natal pathology. Both periods are subjected to the same disorders, although the end results may be very different indeed.

3. *The Heteroplasias*.—There are several closely allied errors of the direction that differentiation has taken, of which those that have occurred during the course of development alone concern us here. The best known are the "upper cardiac glands" of the œsophagus, found at the level of the cricoid cartilage in a high percentage of individuals. Fig. 17 is a drawing of the edge of one of these. The squamous epithelium ends abruptly, its place being taken by a collection of glands which correspond exactly with those of the cardia. Although auto-digestion was well advanced (proving, by the way, that the heteroplasia had secreted a gastric juice), a few oxyntic cells

remain. The glands are superficial to the muscularis mucosæ of the œsophagus.

This heteroplasia can only have originated at the time of development when the entodermal cells became differentiated into those of the œsophagus and of the stomach. For reasons unknown the cardiac character, which is recessive in the remainder of the œsophagus, acquires dominance at the level of the cricoid cartilage in a considerable number of individuals. These and similar anomalies, a considerable number of which could be mentioned, do not postulate a displacement of tissue. It is the cells of the region in which they are found that have

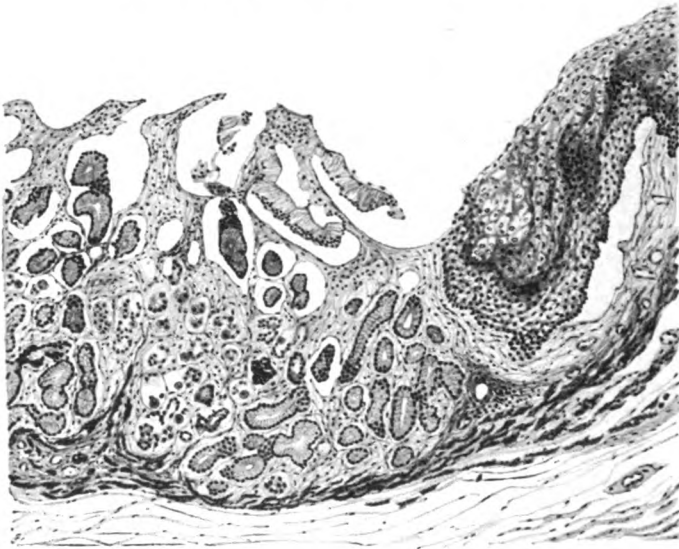


FIG. 17.

Upper cardiac glands of œsophagus. Magnif., 90.

developed into perfectly normal, fully differentiated tissue, whose only anomaly is one of position.

4. *Persistent Embryonic Organs*.—The remnants of the Wolffian body, known as the parovarium, and those of the Wolffian duct in the female are classic examples of the persistence of foetal organs. The former ought perhaps to be regarded as a normal structure. I have never failed to find it in the broad ligaments I have examined, and doubt if it is ever completely absent. Since it exhibits great variations in size in different individuals, it appears to be on the borderland between normal and abnormal persistences in a hypoplastic state, for it represents the epididymis, its homologue in the opposite sex, on a rudimentary scale.



Fig. 18 shows part of a typical parovarium. It is built up of a series of tubules lined by small cubical or columnar cells, often in more than one layer, each of which is surrounded by a fibro-muscular envelope of varying thickness, or sometimes absent. The tubules are collected into groups, held together by the areolar tissue of the broad ligament.

Although the tissues of the parovarium are rudimentary, they show no signs of being undifferentiated, and can at once be recognised as having the orderly arrangement of those of an organ. The tubules produce a secretion, owing to the retention of which they are very liable to become cystic. The cysts are small or large. The latter are of clinical and pathological

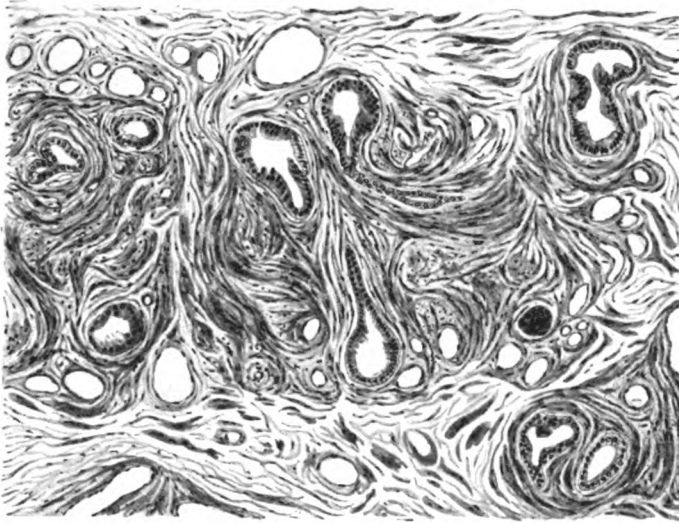


FIG. 18.  
Parovarium. Magnif., 90.

interest, and will be dealt with later. The epithelium of the small cysts often shows signs of proliferation. These are, however, no greater than in other retention cysts, and are due to the stimulating effect of the tension exerted on the epithelium by the accumulation of secretion, which induces them to keep pace with the increase in circumference entailed.

The duct of Gartner, as the Wolffian duct is named in the female, is much more variable in the extent to which it persists. Small, usually cystic remnants of it can be traced, according to Meyer,<sup>14</sup> between the layers of the broad ligament, close to the side of the uterus, to the level of the internal os. Thence it can be followed within the superficial part of the cervix, over the vault of the vagina, and in its lateral wall to the hymen.

I have seen its remnants in the cervix; its lumen was lined by several rows of small cubical cells. In the lower part of the cervix it forms an ampulla which, according to Meyer, is the homologue of that of the vas deferens. I have observed a large cyst of this nature. Its walls were folded and presented branched papillary projections, and were lined by a single layer of cubical or columnar cells.

It is of interest to note that the tubules of the parovarium and the remnants of Gartner's duct in the broad ligament are occasionally lined by squamous epithelium. The assumption of a displacement of cells is unnecessary in these cases, they are correctly explained as anomalies of differentiation.

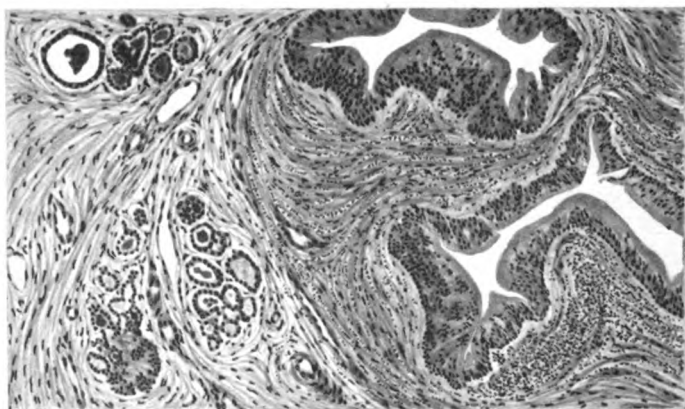


FIG. 19.

Thyro-glossal cyst. Magnif., 85.

Thyro-glossal cysts are instances of abnormal persistence. They are formed by an accumulation of secretion within remnants of the duct of that name. They are found in the anterior middle line of the neck, between the base of the tongue and the thyroid gland, and are perhaps most frequent behind the hyoid bone. They are lined by squamous epithelium, which is sometimes keratinised, or, more frequently, by ciliated respiratory epithelium. Differentiation can proceed beyond this stage, however. This is shown by Fig. 19. The specimen illustrated was removed from the hyoid region of a boy of eight, several months after an unsuccessful operation. Parts of two cross-sections of the duct are seen, surrounded by inflammatory granulation tissue. Its epithelium is hyperplastic and inflamed, being much increased in thickness above the two or three layers which generally form the lining. Near the lower left-

hand corner of the drawing there is a solid mass of epithelium identical with that of the two large ducts, whose cells have in part undergone differentiation into young thyroid alveoli. Two other groups of thyroid vesicles are present, one of which is young, whereas the other consists of small atrophic adult structures.

A good deal of differentiation into thyroid tissue occasionally takes place in these cysts. I have seen two accessory thyroids produced in this way. One was found on the anterior wall of the larynx below the hyoid in a man of forty-six. It measures about a cm. in diameter, and consists principally of an encapsulated nodule of hyperplasia, or an adenoma (I never know

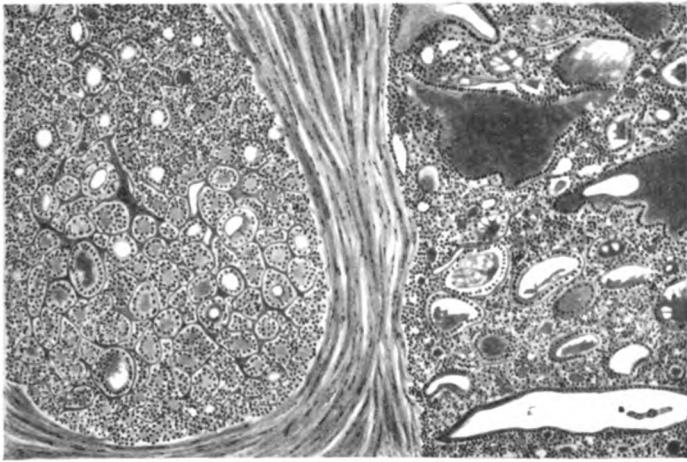


FIG. 20.

Accessory thyroid. Magnif., 90.

what to call these tumours), surrounded by atrophied and compressed thyroid tissue. Since these nodules are common in the thyroid, there is nothing surprising in the presence of one in an accessory organ.

The other case is of greater interest. It measures 2 cm. in length and was removed from behind the hyoid of a girl of nineteen. It consists of lobules of thyroid tissue separated by dense fibrous septa, without signs of inflammation. A few remnants of the duct, lined by a double row of columnar cells, occupy spaces in the fibrous tissue. Fig. 20 shows parts of two of the nodules of thyroid tissue. The smaller one consists of groups of epithelial cells, many of which are solid, whereas others have acquired lumina and contain colloid. It represents the gland at a comparatively early stage of development. There are,

however, no irregularities of the grouping of cells, they are all tending to produce typical thyroid tissue. In the larger nodule, only a small part of which appears in the figure, colloid formation is much more advanced, but the grouping of the cells and the shape of the vesicles is much more atypical than in the other. It resembles the appearances seen in certain hyperplastic adenomata of the gland.

It must be admitted that some of the thyroid tissue in Fig. 19 and the smaller nodule in Fig. 20 present a remarkably embryonic appearance. If I interpret the former figure correctly, it demonstrates that the cells of the thyro-glossal duct that have not been absorbed according to the general rule have retained the capacity to undergo their physiological development. It is, in my opinion, an instance of differentiation of normal type, but retarded. It may be that some stimulus necessary for the conversion of the respiratory epithelium of the duct into secreting thyroid tissue was absent. I do not know what this stimulus was. It may have been provided by the altered blood supply or the inflammation set up at the time of the first operation.

The appearances seen in Fig. 20 can be explained in a similar way. We are not compelled to assume that the thyroid tissue had remained in this undifferentiated "embryonic" state for nineteen years. The hyperplastic condition of the big nodule suggests that there was a demand on the part of the body for more thyroid tissue. The short history supports this view. So does the age of the patient, one at which disorders and enlargements of the thyroid frequently make their appearance. Although there were no symptoms of thyroid insufficiency, it is quite possible that this was a case in which every little helps, and that the persistent piece of thyro-glossal duct was stimulated to take on its embryological function and to differentiate into secreting glandular tissue. Here we would have a stimulus capable of producing such a physiological effect.

Be this as it may be, the fact remains that these two specimens are striking instances of undifferentiated "embryonic" tissues found in childhood and early adult life. But, and this is even more important, these tissues appear to be undergoing an orderly course of differentiation, and display no tendency to proliferate beyond the amount seen in hyperplastic conditions due to some physiological cause.

Duplication of parts and abnormal diverticula of tubes are instances of hyperplasia. Meyer<sup>16</sup> has given an exhaustive account of these. I will do no more than mention that many mesenteric cysts are produced in this way. They are lined

by intestinal or by squamous epithelium, and their walls contain a varying amount of plain muscle.

Many more instances of anomalies of bulk and of differentiation could have been given, but these will suffice. In the next study I propose to discuss the most important of the tissue malformations that are caused by errors of position, and in which displacement is often a prominent feature.

### *Conclusions.*

Tissues that are found in abnormal positions as the result of an error of development have not necessarily been displaced. In the instances considered they have arisen *in situ* as anomalies of bulk and of differentiation.

The cells of tissue malformations undergo their differentiation at the same time as the normal tissues. At most they lag behind to a slight extent. In exceptional circumstances their physiological development is retarded. They show no signs of persistence in an "embryonic" state, or of active proliferation beyond that seen in normal organs as a result of stimulation by inflammation, the needs of the body, and other physiological causes: of their environment, in other words.

In the rare instances in which an accessory glandular organ presented an "embryonic" appearance, the assumption is probably correct that it had only recently begun to be differentiated in a regular, physiological manner from the simpler cells of the original malformation.\*

\* Undifferentiated "cell-rests," as postulated by Cohnheim's theory, are extremely rare, and have only been found later than the first few months of extra-uterine life in cases of tuberous sclerosis. It is their usual fate to disappear.

Why these cell-rests should persist only in the malformations of tuberous sclerosis, whereas they invariably disappear in all others, adds one more to the many obscure problems of this mysterious disease.

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# SPONTANEOUS RUPTURE OF THE SPLENIC VEIN IN A CASE OF ENLARGED LIVER AND SPLEEN

## WITH NOTES ON THE CITRATE METHOD OF TRANS- FUSION, AND THE POSSIBILITIES OF AUTO- TRANSFUSION

By W. H. OGILVIE, M.Ch., Surgical Registrar, Guy's Hospital.

DURING 1919, when we were both on the staff of the Military Orthopædic Hospital, I had several conversations with Mr. H. H. Sampson of the General Hospital, Birmingham, on the methods of blood transfusion used during the war. He told me that he had, while in France, conceived the idea of collecting blood found free in the peritoneal cavity in cases of abdominal gunshot wounds, and transfusing the patient with his own red cells, but had been unable at the time to carry out this idea in practice. In September 1921 I had to operate on a case, in which the procedure suggested by Mr. Sampson seemed to offer a chance, though an infinitely slender one, of saving life. The result, while unsuccessful, convinced me that we have in auto-transfusion a method which has a definite place in surgery, and one which may possibly turn the scale in favour of the patient in an apparently hopeless case.

### *Spontaneous Rupture of the Splenic Vein in a Case of Enlarged Liver and Spleen ; Splenectomy ; Death*

F. R., a clerk, aged thirty-one, was admitted into Guy's Hospital under Dr. Herbert French on the 8th of September, 1921. At the age of fifteen he had "jaundice and an enlarged liver." For the last eight or nine years he had had "liver attacks" every two or three months. During these attacks he became yellow and his urine was dark in colour, but his stools were not clay-coloured. He did not feel really ill in the attacks, which only lasted a few days. Latterly his complexion was always yellowish, even between attacks.

During July and August 1921 he had two attacks, in which, in addition to the above symptoms, he became breathless and had sharp pains over the liver and in both sides. Both these attacks lasted only a few days.

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*Condition on admission.*—There was a distinct yellowish tinge about the skin, mucous membranes, and conjunctivæ. The liver extended nearly as far as the umbilicus. The spleen came well below the umbilicus, reaching at its lowest point a line drawn from the umbilicus to the left anterior superior spine of the ilium. No free fluid could be detected in the abdomen.

*Blood examination :*

Hæmoglobin . . . . .	90 per cent.
Red cell count . . . . .	5,680,000 per cub. mm.
White cell count . . . . .	2,800 per cub. mm.
Differential white count . . . . .	Normal.

*Urine.*—Contained urobilin and traces of bile pigments.

*Progress.*—On September 22 at 7 p.m. the patient began to be restless, and complained of a feeling of distension in the abdomen, but there was no actual pain. At 10.45 p.m. he began to vomit, became much more restless, and would not lie down. The pulse was now 96. The abdomen was markedly distended, and showed movable dullness and a fluid thrill. At 11.45 p.m. the restlessness was still more marked, and the abdomen was extremely tense. A small trocar was plunged through the parietes on the left side about one inch above the iliac crest, and what appeared to be pure blood spurted out under considerable pressure. As the spleen was known to be large, it was thought that this might have been entered. Two more punctures were therefore made on the right side of the abdomen, and on each occasion revealed blood. The pulse was now 110.

*Operation.*—I saw the patient at midnight with Dr. J. A. Ryle. He was now very pale, anxious-looking, with a cold clammy skin, air hunger, and great restlessness. It was obvious that an immediate laparotomy to find the source of the bleeding offered him his only chance, and equally obvious that he could not be touched without a preliminary transfusion. As his relatives lived at Tunbridge Wells, and as immediate action was imperative, I decided to try auto-transfusion, being influenced by the knowledge that his abdomen contained a large amount of fluid blood.

At 12.30 a.m. Mr. Bonar gave gas and oxygen, and a left-sided Kocher's paracostal incision was made down to the peritoneum. A stab was then made into the peritoneum, and the jet of blood which spurted out was caught in a pint measure containing sodium citrate. After this a further  $2\frac{1}{2}$  pints were caught in a sterile basin containing sodium citrate solution. As the flow of blood seemed now faster than ever, the wound was rapidly opened, and the hand plunged into a pool of blood. Dr. Ryle meanwhile started running the blood which had been collected into the patient's right median basilic vein. I quickly found that grasping the splenic pedicle arrested the gush of blood. Further investigation being out of the question, I therefore carried out a splenectomy, being considerably hampered by the size of the spleen, and by dense adhesions



between it and the diaphragm. The diaphragmatic adhesions were ligatured off. The clamps were, however, left on the pedicle of the spleen, and the abdomen rapidly closed. The operation lasted about thirty-five minutes.

The patient's condition started to improve as soon as transfusion was commenced. He was, however, profoundly shocked, and restlessness returned as soon as he started to come out of the anæsthetic. He died at 5 a.m.

*Post-mortem.*—The spleen was fibrotic, and weighed 640 grammes. There were no lacerations, and no torn vessel was found anywhere in the abdomen. The fact that clamping the splenic pedicle arrested the hæmorrhage may therefore be taken as proof that the blood came from a large vessel in the pedicle itself, probably the vein.

The liver was enormously enlarged, and everywhere contained nodules, the largest of which was the size of a tangerine orange. These were lighter than the rest of the liver and greenish in colour.

Both lungs showed small hard nodules scattered throughout their substance.

*Microscopic sections.*—The spleen showed extensive fibrosis only.

The liver showed cirrhosis, on which was implanted a primary hepatic carcinoma with large darkly staining hepatic cells arranged in irregular lobules.

The nodules in the lungs showed neoplastic cells arranged and grouped in hepatic fashion.

#### *Indications for Auto-transfusion*

This case demonstrates that it is certainly possible in an emergency to make use of the patient's own effused blood for purposes of transfusion, provided only that a 2½ per cent. solution of sodium citrate in normal saline, or the materials for making such a solution, are kept in readiness. Where such a solution is available, auto-transfusion can be applied whenever a collection of uncoagulated blood is discovered during operation on a case of hæmorrhage. This will undoubtedly be an infrequent occurrence. It will probably only be found in cases where bleeding has occurred into the large serous cavities. The blood in penetrating wounds or injuries of the abdomen will usually be contaminated with intestinal contents. However, traumatic rupture of the spleen and traumatic hæmothorax suggest themselves as conditions where auto-transfusion might easily turn the scale in favour of survival in an exsanguined case.

#### *Other Methods of Transfusion*

Blood transfusion has now been placed on a secure footing as one of the most valuable of all remedial measures at our

disposal. The different conditions in which its value has been established beyond question, and still more the conditions in which its use has been suggested and occasionally employed, are now so numerous, that we are apt to lose sight of the fact that there is one condition in which its importance is supreme. That condition is a severe primary hæmorrhage due to trauma. In allowing our interest to stray to conditions in which the value of blood transfusion is less direct, such as the anæmias or chronic toxic states, we have been inclined to assess the alternative methods open to us more by their theoretical soundness than by their practical applicability. Traumatic primary hæmorrhage is a condition that may occur absolutely unforeseen in the most remote places and among the most unpropitious surroundings. It is specially apt to occur in the youngest, most active, and healthiest of men, and therefore those in whom a death that could possibly be averted is a tragedy of the first magnitude. Immediate blood transfusion offers, in a severe case, the only hope that such a calamity can be avoided. A method which can be applied under such conditions must be possible to carry out with no special apparatus, no assistance, no technical skill, and must be one that cannot fail. The only method satisfying these requirements is the "jug and funnel" citrate method.

Methods of blood transfusion fall roughly under three headings: the direct, vein to vein or artery to vein; the indirect, by syringe or paraffin-coated vessels; and the citrate methods. The methods in the first and second groups demand rapid work, a certain degree of technical skill, and the impedimenta of a surgical operation, and in both failures cannot be entirely eliminated. In the less urgent conditions calling for transfusion, where the time and place can be chosen, and where a failure will not mean a healthy life thrown away, the ideal method is probably the transference of whole blood by means of a paraffin-coated vessel. The citrate methods demand less speed, but many of them require a delicate technique, and the possession of a special apparatus which has to be sterilised beforehand in the autoclave. In a matter of life and death there is no time to summon the expert and his outfit. For the "jug and funnel" method, the only requirement which cannot be improvised in an emergency is a known quantity of sodium citrate, and on these grounds it is a method which should be familiar to every one who may be called upon to treat a sudden hæmorrhage—that is, to every medical man.

In hospital practice a 2½ per cent. solution of sodium citrate in normal saline can be kept ready in sterile flasks. For emergency use, a packet or compressed tablet containing sodium

citrate 2.5 grammes, sodium chloride 0.9 grammes, is added to 100 c.c. of water, and the solution boiled for ten minutes. Where a donor is available, the citrate solution is poured into a sterile graduated flask standing in a bowl of water at 140° F., which is then placed under the arm of the donor. Into the citrate solution four times its volume of blood is run, making a strength of 0.5 per cent. citrated blood. If it is desired to transfer about a pint of blood, the whole 100 c.c. is put into the measured flask, and blood run in to 500 c.c. If a greater or smaller amount is required, more or less of the citrate solution is used. This citrated blood will remain unchanged if kept warm, and can be transfused into the recipient's vein at any time within an hour or two of drawing it off. This is done through a tube and funnel connected to the needle of a saline infusion apparatus.

The simplest method of taking the blood is by means of a short, wide, straight needle, the diameter of a No. 8 catheter, some of which have been made for me by Down Bros. Six inches of Carrel size rubber tubing is slipped over the end of the needle, and a little liquid paraffin run through the lumen. The needle is then plunged into the median basilic vein of the donor while his arm is held over the measured flask, the rubber tubing serving to direct the stream of blood. With a wide-bore needle of this type the clotting which occurs is never sufficient to stop the flow, and the 400 c.c. of blood are obtained in three to five minutes. Careful asepsis is, of course, essential. In an emergency the vein may be cut directly with a scalpel, while the measured flask can well be improvised and sterilised.

The question of the hæmolytic group of the donor presents a difficulty in emergency transfusion. The test sera are, however, so easily kept, and their employment is so rapid and simple, that a grouping can nearly always be done before a donor is decided upon. Given a healthy donor, especially if it be a brother or sister, the jug and funnel method justifies an emergency transfusion even without grouping. There is no call for speed in the citrate, as there is in the paraffin-tube methods. If a preliminary grouping of the donor has not been possible, half a pint of normal saline is first run into the recipient's vein through the funnel, and the citrated blood is then run in at the rate of about one ounce in three minutes. If there be incompatibility, symptoms will appear within ten minutes in the shape of a feeling of constriction in the chest and pains in the back, and the transfusion must be stopped, and normal saline or gum acacia solution substituted for the remainder of the blood.

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The simplicity of the method has this further advantage, that it allows the same operator single-handed to withdraw the blood and put it into the patient, while blood may be taken in any place where the conditions and lighting are suitable, and transported to the bed or stretcher of a patient whose life might be endangered by any movement.

I am much indebted to Dr. Herbert French and to Mr. Hodgkinson, the Clinical in charge of the case, for permission to publish these notes.

## FREQUENCY OF ANTRAL INFECTION IN CHILDREN

By W. M. MOLLISON, C.B.E., M.Ch., F.R.C.S., and N. E. KENDALL  
(From the Ear and Throat Department, Guy's Hospital.)

ATTENTION has been drawn to the subject of suppuration in the maxillary antrum in children from time to time, and opinion has been divided on the frequency with which it occurred. In the experience of one of us (W. M. M.) several cases had been seen. Sir St. Clair Thomson states that maxillary sinusitis in children is rare. It was therefore decided to investigate a series of children with a view to discovering in what percentage it was present.

The investigation was carried out in February and March 1921; the children chosen were those attending the Ear and Throat Out-Patient Department at Guy's Hospital. A large proportion of these are children belonging to the L.C.C. schools, who are referred for treatment of various catarrhal affections of the upper respiratory tract, for deafness, or suppurative otitis media. The bulk of these children require removal of adenoids, or tonsils and adenoids, and it was a series of these cases chosen for operation on whom the investigation was carried out.

All the cases exhibited symptoms of nasal catarrh or pharyngeal catarrh—frequent colds, snoring, indistinct speech, mouth-breathing, sore throats, ear-ache, and deafness from time to time, or otorrhœa; but only in a small number were signs of pus seen in the nose. Their ages were from two to sixteen years. A series of 102 children was investigated. The operations were performed in the Out-Patient Department. An anæsthetic was given, and a large-bore, curved needle, fitted to a syringe, as suggested by Watson-Williams, was passed into each antrum and through the inferior meatus of the nose and the contents withdrawn. Two or three needles were at hand and a fresh needle used for the second antrum should the first have found pus or muco-pus.

The adenoids, or tonsils and adenoids, were removed after the punctures, and the bleeding from the nose was not found

to interfere with the operation to any extent. As was to be expected, the anæsthesia had to be somewhat prolonged, but in no case did any untoward symptoms result. The introduction of the needle was not always easy, especially in young children. It was facilitated, however, by the following technique: the point of the needle was directed straight into the nostril, then made to skirt the outer lower angle and so inserted under the inferior turbinate; the point was then turned upwards till it aimed, as it were, at the external canthus of the eye and was then driven outwards through the bony wall into the antrum. When this procedure was adopted the antrum was always entered even by previously inexperienced dressers. The procedure adopted by Watson-Williams is to syringe some sterile water into the antrum and subsequently to withdraw it; by this means very small amounts of muco-pus can be discovered and bacteriological examinations made of the fluid; but in this series of investigations no water was injected, aspiration alone was used. In order to detect small amounts of fluid from the antra, the head was turned to the side so that the needle-point was at the most dependent part of the antrum; the piston of the syringe was then withdrawn. In most cases air only was drawn into the syringe; in some cases a few drops of sticky muco-pus were withdrawn, and in other cases the piston could not be withdrawn or a drop of blood appeared at the entrance to the syringe. In these cases suction was maintained; the syringe and needle were then removed from the nose, the contents of the needle were expelled into a basin, and thus small amounts of muco-pus, enough only to fill part of the needle itself, could be readily detected.

On two occasions the operator failed to pass the needle into the antrum, apparently because the bone was so thick, or perhaps because there was no antrum developed. On one occasion the point of the needle was not passed far enough into the nose, and on being turned outwards it appeared under the soft tissues of the face; beyond a bruise for a few days no harm followed.

In one case the child developed a "black eye" after puncture, perhaps from damage to the orbital wall of the antrum; the extravasation had all disappeared in a week's time.

Of those in which nothing was found on exploration one was unsatisfactory at the next attendance and was not seen again, and one had unilateral nasal obstruction which cleared up in fourteen days.

The results revealed great frequency of infection in the antra; thus among the 100 cases 22 showed muco-pu., or pus

in one or both antra. Distinction is made between creamy pus and sticky muco-pus. The presence of the latter seemed to lead to no clinical manifestations. After removal of adenoids, or tonsils and adenoids, the child lost all catarrh and seemed well. Even in cases where pus was found, the child became well after removal of tonsils and adenoids.

The results may be tabulated thus—

Muco-pus or pus in one or both antra . . . . .	22
Muco-pus in one or both antra . . . . .	16
Pus in one antrum . . . . .	4
Pus in one antrum and muco-pus in the other . . . . .	2
Pus in both antra . . . . .	2

In one case yellow fluid was found in one antrum.

The number of cases investigated was 102, so that the results are percentages to all intents and purposes.

It is clear from the results of these punctures that of children suffering from catarrhal affections of the nose and throat a considerable proportion have infection of the antra and possibly therefore of other nasal accessory sinuses; the subsequent history shows that after removal of tonsils and adenoids, or adenoids alone, recovery follows in the majority of cases.

It is very probable that the presence of antral infection is an important factor in producing nasal obstruction in children; it is only in a very small percentage of children that adenoids produce obstruction solely by their bulk. In the majority, obstruction is due to the consequent nasal catarrh, and it is well recognised that any infection of the antra causes nasal obstruction by infection and swelling of the nasal mucous membrane.

The discovery of muco-pus on exploration does not give an indication for opening the antrum into the nose, since it has been shown that the patients recover from symptoms after removal of the adenoids, or tonsils and adenoids; indeed, recovery may follow even if creamy pus is found in the antra (*vide* cases 14, 37 and 45).

The cases in which creamy pus was found emphasise the importance of investigation of the antra in nasal and nasopharyngeal catarrh in children, especially when removal of tonsils and adenoids has failed to effect a cure. Cleminson has written about cases of this kind in the *Journal of Laryngology* for December 1921.

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### *Conclusions.*

1. Infection of the antra occurs in over 20 per cent. of children with naso-pharyngeal catarrh.

2. Removal of adenoids, or tonsils and adenoids, effects a cure in most cases.

3. Antral suppuration must be excluded as a possible cause of nasal catarrh in children, especially in those whose tonsils and adenoids have been removed.

4. Puncture of the antra is not followed by any ill-effects.

### RESULT OF CASES IN WHICH PUS OR MUCO-PUS WAS FOUND

No. in series	Sex.	Age.	Condition of antrum.		Other operation performed.	Result.
			Right.	Left.		
1	F.	10	Nil.	Muco-pus.	Ant. end of R. middle turbinal removed on account of enlarged cell.	Well.
7	F.	12	Little muco-pus	Nil.	Removal of tonsils and adenoids.	Well.
14	F.	10	Much pus.	Muco-pus.	Removal of adenoids.	Well.
18	M.	5	Muco-pus.	Nil.	Tonsils and adenoids.	Did not attend.
22	M.	6	Slight muco-pus.	Nil.	Tonsils and adenoids.	Seven months later pus in L. side of nose.
26	M.	12	Pus.	Nil.	Tonsils and adenoids.	Did not attend.
28	M.	13	Slight muco-pus.	Nil.	None.	Attended twice, was improving: not well.
30	M.	6½	Yellow jelly-like muco-pus.	Muco-pus.	Tonsils and adenoids.	Well in one month.
37	M.	12	Considerable pus.	Nil.	Adenoids.	Well.
45	M.	12	Nil.	Pus.	Tonsils and adenoids.	Probably well.
46	M.	3½	Muco-pus.	Slight muco-pus.	Adenoids.	Well in fourteen days.
47	F.	3	Slight muco-pus.	Nil.	Adenoids.	Well.
55	M.	4	Slight muco-pus.	Nil.	Adenoids.	Well.
59	M.	9	Pus.	Nil.	Tonsils and adenoids.	Well.
61	F.	14	Nil.	Two c.c. clear yellow fluid.	Tonsils and adenoids.	Well.
62	F.	14	Pus.	Pus.	Intranasal opening of R. antrum.	Not well.
66	M.	7	Nil.	Muco-pus.	Tonsils and adenoids.	Well.
70	F.	10	Muco-pus.	Nil.	Tonsils and adenoids.	Did not attend.
72	F.	5	Muco-pus.	Slight pus.	Tonsils and adenoids.	Well.
91	M.	8	Muco-pus.	Muco-pus.	Adenoids.	Did not attend.
100	M.	4½	Slight muco-pus.	Muco-pus.	Tonsils and adenoids.	Did not attend.
102	M.	8	Muco-pus.	Muco-pus.	Adenoids.	Well.

### *Summary.*

Well . . . . . 14

Did not attend again . . . . . 5

Not well, 4 (of whom 1 was operated on for antral suppuration by the intranasal route).



## SEPTICÆMIA IN OTITIS MEDIA AND ITS COMPLICATIONS

By C. GILL-CAREY. (From the Ear and Throat Department, Guy's Hospital.)

THE interest in the results of blood cultures in suppurative otitis media and its complications has arisen chiefly in connection with septic thrombosis of the lateral sinus. A high percentage of these cases yields a positive blood culture, and it was considered by some otologists that the mere presence of bacteriæmia in a case of suppurative otitis was evidence of septic thrombosis.

In 1909 Duel and Wright published the results of blood cultures in fifty-five cases of suppurative otitis in the Manhattan Eye and Ear Hospital. Positive results were obtained in fourteen cases; of these four had septic lateral sinus thrombosis and one had suppurative labyrinthitis and meningitis, while eight were cases of uncomplicated mastoiditis and one was a case of acute suppurative otitis media without complications. In many of these last nine cases there was no clinical evidence of a blood infection.

In a paper read before the Otological Section of the Royal Society of Medicine in 1918, Lake reported three cases of acute mastoiditis with severe constitutional disturbance in which bacteriæmia was demonstrated.

In twelve of the cases cited by Duel and Wright the infecting organism was a streptococcus, and in two a pneumococcus. In Lake's cases streptococci were found in all three.

Of the cases reported below, Nos. I. and II. illustrate the severe type of general infection, which may follow uncomplicated acute suppurative otitis media. In the second case no positive blood culture was obtained in spite of the clinical signs present. Case III. is one of unrecognised lateral sinus thrombosis.

### *Case I.—Acute Otitis Media with Bacteriæmia*

Ethel P. was admitted on September 20, 1921, with a history that a fortnight ago she had severe sore throat, which was

followed in two days by ear-ache on the right side. Although complaining of ear-ache occasionally, she was able to attend school until September 16, when she complained of severe pain in the ear and was thought by her mother to be feverish. She was then kept in bed and attended by her doctor, who ordered drops for the ear. Her general condition became worse, and on the morning of the 20th she had a rigor and was sent to hospital by the doctor with a provisional diagnosis of lateral sinus thrombosis.

On admission her temperature was  $103.2^{\circ}$ . She was irritable, and resented examination, but was quite clear mentally. She complained of pain in the right ear and headache.

Both tonsils were found to be large and inflamed, with debris in the crypts. The naso-pharynx was not examined.

The right membrane was dull red and moderately bulging. There was no swelling of the meatus and no mastoid tenderness. The left ear was normal.

There was very slight tenderness over the upper part of the right sterno-mastoid muscle, but movement of the neck was free and painless. There were signs of bronchitis.

There was no abnormality in the nervous system; the discs were examined and found normal.

Myringotomy was performed and clear fluid was obtained. Twenty c.c. of anti-pneumococcal serum were given subcutaneously. No change occurred as a result of these measures. The temperature varied from  $99^{\circ}$  in the morning to  $104^{\circ}$  or over in the evening. There was a profuse purulent otorrhœa, gradually lessening in amount after three or four days. No signs of mastoid involvement appeared, but on September 28 it was decided to explore.

On opening the mastoid a little muco-pus was found in the antrum, but no disease in the mastoid air-cells, and the dura of the middle and posterior fossæ was healthy. The wound was closed by primary suture after smearing with B.I.P. paste.

The evening temperature on the day following operation was  $104.3^{\circ}$ . A blood culture taken then yielded a free growth of streptococcus longus, and the same organism was grown from an antral swab taken at the operation.

Having first desensitised the patient, anti-streptococcal serum was given for six days, 20 c.c. being injected daily. In spite of using polyvalent sera of different brands no good effect was seen; the ear discharge rapidly ceased, but the temperature remained high and the child's condition appeared desperate.

About October 1 she complained of pain in the right arm over the lower part of the triceps, where it was said she had had an injection of morphia on the day of admission. A radiograph of this region showed a shadow in the muscle and an area of periostitis underlying it. An operation was performed and an abscess was found in the triceps. There was a small area of periostitis in continuity, but no infection of the bone.

Streptococci were grown from a swab taken at the operation.

An initial dose of half a million streptococci was given at this time from an autogenous vaccine prepared from the blood culture.

Two days after the last operation the temperature began to show signs of settling down, and by the middle of October it remained steadily at normal.

On November 13 the patient was discharged; the right membrana tympani was normal and hearing was perfect. A few adenoids were seen and the tonsils appeared slightly infected. It was arranged to remove the tonsils and adenoids after convalescence.

*Case II.—Acute Otitis Media with Septicæmic Symptoms*

Mary F., aged 7 years, was noticed to be very sleepy on August 21, and on the 23rd fell asleep while at school. She was then kept at home, and remained in the same sleepy condition until her admission. She would answer questions, but immediately became sleepy if left alone. On September 11 it was noticed that her left ear was discharging. A letter from her doctor stated that throughout the illness her temperature had varied between 100° and 103°; beyond some signs of infection at the left apex and a trace of albumen in the urine he found nothing to account for her condition.

On admission the child answered questions rationally and was able to sit up. Examination showed moist sounds at the left apex, and early optic neuritis, but no other abnormality of the nervous system. There was pus in the left meatus and the introduction of a speculum was painful. The drum was red. Lumbar puncture on the 16th gave normal fluid. An x-ray examination of the chest was negative. Examination of the blood gave a count of 3,392,000 red cells per cub. mm.; the hæmoglobin percentage was 50.

There was no change in the patient's condition by the end of September; the temperature had remained high, and she was still sleepy. Further investigation had thrown no more light on the subject. A Widal reaction had been negative.

On September 28 a meatal boil was opened on the left side and a second lumbar puncture was done; the fluid obtained was normal.

The eyes were examined again on the 29th, when there was less neuritis; no papillœdema, hæmorrhage, or tubercles were seen.

Dr. French at this time considered that the child's symptoms were due either to a source of infection in the ear, or to encephalitis lethargica or to some undiscovered general infection, such as typhoid fever.

Mr. Mollison, who saw the patient in consultation on October 1, considered that the mastoid should be opened in view of the continued suppuration in the middle ear. On the 3rd he explored the mastoid, but beyond some pus in the

antrum nothing was found. The lateral sinus and the dura exposed in the middle and posterior fossæ were healthy.

A lumbar puncture was again done; the Wassermann reaction was negative and no micro-organisms were grown from the fluid.

A blood culture on the 18th was negative.

No fall in temperature occurred until the 25th, when the child began to improve.

### *Case III.—Lateral Sinus Thrombosis with Septicæmia*

Mercia H., aged 12 years, was admitted on November 1, 1921. Ten days before admission she had complained of ear-ache on the right side; the pain was not severe and she had attended school up to the week before admission. In this week she had become increasingly drowsy and had continuous headaches and pains in the limbs. She had been delirious for the last two nights. No discharge from the ear had been noticed.

On admission the temperature was 103·2°; the child was in a typical "typhoid state." She was drowsy and answered questions badly.

The tonsils were enlarged but not inflamed. There was a mass of adenoids. The right membrana tympani was red and bulging. There was no mastoid tenderness and no pain in the neck. The discs were normal. Moist sounds were heard in both lungs.

Myringotomy on November 1 gave a small amount of turbid fluid, from which a hæmolytic streptococcus was grown. Flood taken on November 2 with the temperature at 104° grew the same organism on cultivation. Lumbar puncture gave normal fluid. The right ear discharged freely for a few days; the discharge then began gradually to lessen; by the middle of the month the ear was nearly dry and the drum no longer red.

On November 6 arthritis of the right wrist and left ankle appeared. Aspiration of the ankle yielded pus, from which a streptococcus was grown. On the 7th the patient had a rigor and another on the 10th. Anti-streptococcal serum was given intravenously, 30 c.c. daily, without effect.

The initial bronchitis became gradually worse, and areas of consolidation appeared at the bases. No mastoid tenderness was elicited at any time, but the patient was so drowsy at most times that moderate pain did not rouse her.

She died on November 20, after a terminal exacerbation of her respiratory symptoms.

Post-mortem examination showed pus in the mastoid air-cells and a large septic thrombus in the lateral sinus. There was early pericarditis and extensive broncho-pneumonia.

### CONCLUSIONS AS TO TREATMENT

In the first case serum therapy was quite unsuccessful. The rapid improvement noticed after the evacuation of a metastatic

abscess might point to the advisability of producing a fixation abscess in similar resistant blood infections.

Lake limited the term "aural bacteriæmia" by including only those cases of mastoiditis and suppurative otitis which had no intra-cranial complications. This classification, however, does not aid in the problem of deciding on a line of treatment, as it would seem advisable in all cases of suppurative otitis presenting constitutional disturbance and bacteriæmia to explore the mastoid and lateral sinus.

## PAROXYSMAL TACHYCARDIA

By G. H. HUNT, M.D., Physician to Guy's Hospital.

ON looking through the index of the medical reports at Guy's Hospital for the years 1900–1915 I only find the occurrence of paroxysmal tachycardia noted five times, and it might be supposed from this that the condition was a comparatively rare one. During the three years following the war I have seen myself eight cases in hospital practice, and additional ones have been recorded in patients under the care of other physicians at Guy's. It is unlikely that the disease has become so much more common recently, and the apparent difference in its incidence is almost certainly due to the fact that it is more frequently recognised now than formerly. Accurate diagnosis is always desirable, but this is particularly the case in a disease like paroxysmal tachycardia, where much can be done to alleviate the symptoms when once their significance is recognised.

### DEFINITION OF PAROXYSMAL TACHYCARDIA

Lewis<sup>1</sup> defines paroxysmal tachycardia as “an affection in which from time to time and for variable periods the natural heart rhythm becomes submerged, and the heart responds to impulses formed at a more rapid rate in some other portion of its walls.” This definition accurately describes the pathological mechanism of the disease, although it does not specifically state its clinical characteristics.

As the purpose of this paper is to give an account of its clinical features, a clinical description is necessary at the outset. In paroxysmal tachycardia the heart rate changes abruptly to a more rapid rate; it continues beating at this rapid rate for a variable period, and then quite abruptly the rate becomes slower. These attacks of rapid heart rate occur at very varying intervals; sometimes several occur in one day, sometimes the intervals between them may be several months. The most characteristic feature of the attack is the suddenness of its onset and its termination; in physiological tachycardia, such as occurs in a man taking a minute's vigorous exercise, the pulse rate rises gradually; it starts, let us say, at 74, rises to 96 at the

end of fifteen seconds, to 120 at the end of thirty seconds, to 140 at the end of a minute; if the man now rests the pulse rate slowly falls, reaching 122 at the end of fifteen seconds, 112 at

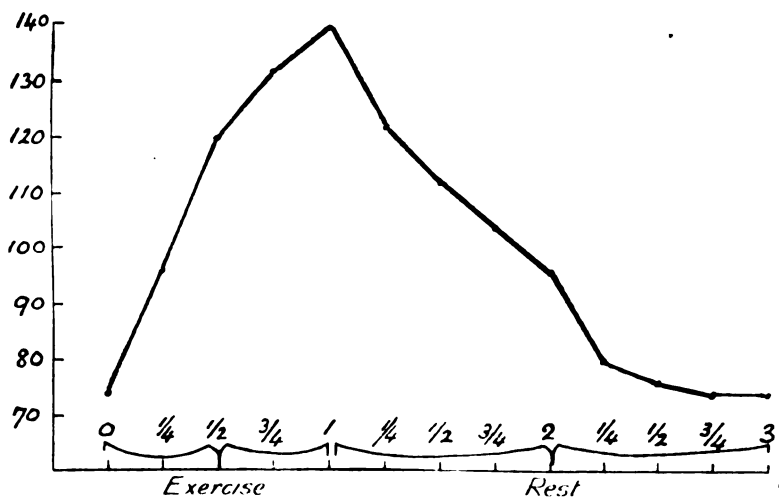


FIG. 1.

The ordinate gives the pulse rate per minute; the abscissa the time in minutes. The figure shows the gradual rise of pulse rate during exercise, and the gradual fall after exercise.

the end of thirty seconds, and finally reaching its original rate at the end of two minutes' rest. These alterations in pulse rates, taken from an actual observation, are represented diagrammatically in Fig. 1. In Graves' disease again the change

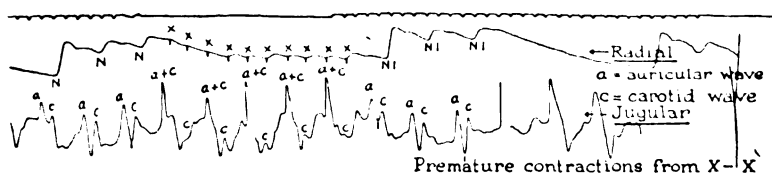


FIG. 2.

Radial and venous pulse tracings showing three normal beats (N-N) followed by a short paroxysm of ten beats of a much faster rate (X-X), followed by three normal beats (N1-N1). The beats of the paroxysm are of such small volume that they only just appear on the radial tracing in its later part, and do not appear at all in its earlier part; their position in the earlier part can be calculated from the venous pulse tracing. The ventricular rate changes abruptly from 90 (N-N) to 160 (X-X), and falls again abruptly to 90 (N1-N1). Electrocardiograms confirmed this interpretation of the venous pulse tracing. Owing to the small volume of blood reaching the brain during the paroxysm the patient experienced sensations of faintness and giddiness.

of pulse rate is gradual; if the patient is getting worse, we see the pulse rising from day to day, and as the patient improves there is a gradual fall. Fig. 2 shows the abruptness of the

change of rate in paroxysmal tachycardia; the rate changes quite suddenly from 90 to 160 per minute; almost instantaneously a new and much more rapid rate begins, which after persisting for about three seconds, returns equally quickly to the original slow rate. Fig. 3 shows the changes diagrammatically, and the sharp rise of the pulse rate, the plateau during the period of tachycardia, and the abrupt fall, are in sharp contrast to the gradual rise, the sharp peak, and the slow fall in Fig. 1.

#### CLINICAL FEATURES OF THE ATTACK

The pulse rate during the attack is always raised; I have seen it over 280—the exact rate was impossible to count with the stethoscope—in a case that proved fatal, but the average rate

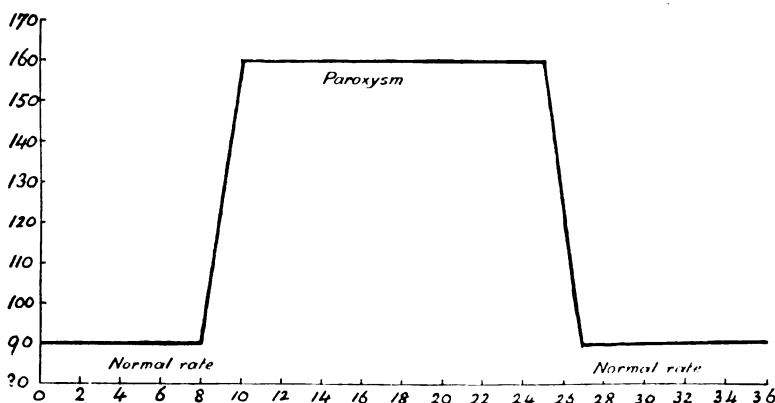


FIG. 3.

The ordinate gives the pulse rate per minute; the abscissa the time in fifths of seconds. The figure shows the abrupt change from a normal rate to a more rapid rate, the persistence of the rapid rate, and the abrupt return to the normal rate.

is 160–200. Occasionally it is under 160, and I have recorded one case,<sup>2</sup> where an electrocardiogram showed that the condition was a true paroxysmal tachycardia, where the pulse rate was only 150 during the attack.

The duration of the attacks is very variable. In the case of the patient, whose pulse is shown in Fig. 2, the tachycardia only lasted a few seconds, but in most cases it continues for a few hours; exceptionally it may persist for several days, and I know of a case where it lasted nearly two weeks.

The symptoms also vary very much. Occasionally the patient is quite unconscious of any alteration in the action of his heart, but as a rule he complains of some cardiac discomfort, which he often describes as palpitation, and this may be associated with slight pain, breathlessness, or flatulence. In other cases



the symptoms are much more serious, and an explanation of this is found by a study of Fig. 2. It will be noticed that during the period of tachycardia the volume of the pulse is considerably diminished; with this diminution of volume there is a fall of blood pressure. This drop of pulse volume and blood pressure, if continued long enough, causes a gradual failure of the circulation. Pallor of the face occurs, and this may be followed by cyanosis and engorgement of the veins of the neck; œdema appears in the extremities, the liver enlarges, the lungs become engorged and œdematous, and cough becomes urgent with copious expectoration, which is sometimes blood-stained. The breathing grows more and more distressed, and in short the picture becomes one of acute cardiac failure, which sometimes, if the attack continues, may terminate fatally.

#### THE DIAGNOSIS OF PAROXYSMAL TACHYCARDIA

Paroxysmal tachycardia should always be suspected in a patient with a regular pulse rate of 160 or over, unless there is an obvious cause, such as an acute infection or Graves' disease, to account for it. Apart from paroxysmal tachycardia it is very rare to find a pulse rate of over 160 in cardiac failure, except in cases of auricular fibrillation, in which case the pulse is irregular in rhythm, volume, and tension. There is one very characteristic feature distinguishing paroxysmal tachycardia from tachycardia of some other origin. In the former the pulse rate is not altered by change of posture; if we find the pulse rate 180 when the patient is standing, and the same rate when he is lying down, we can be certain of the diagnosis. Even in the more severe attacks, where the condition of the patient precludes his standing, this test can usually be applied by moving him from the recumbent to the sitting position. Another very suggestive feature is the constancy of the pulse rate throughout the attack; this serves to distinguish paroxysmal tachycardia from tachycardia of nervous origin; in emotional tachycardia the pulse varies every few minutes, and alterations of ten beats or so per minute, together with other evidence of neurosis, make the distinction from paroxysmal tachycardia easy. Occasionally we are fortunate enough to see the beginning or the end of an attack. This was the case in a patient on whose chest a hot fomentation had been put to relieve precordial pain; two minutes after its application the pulse dropped abruptly from 160 to 80. This sudden change of rate made the diagnosis of paroxysmal tachycardia certain, and I subsequently took electrocardiograms which were typical of the condition.

If the patient is seen during an attack, the diagnosis can

generally be made, if attention is paid to the points mentioned above. It is very much more difficult to arrive at a diagnosis if the patient is only seen during the intervals between the attacks. A history of attacks of palpitation or "fluttering" in the chest (patients often use the word "fluttering" to describe the sensation experienced during an attack), coming on suddenly and terminating suddenly, is suggestive; a sudden termination particularly is an important point, for although the palpitation that arises from indigestion or other cause may start suddenly, the patient usually tells us that relief comes gradually. In many subjects of paroxysmal tachycardia extra systoles are present in the intervals between the attacks, and if these are shown to be auricular in origin by electrocardiographic or polygraphic examination, their presence is in favour of paroxysmal tachycardia, although it does not make the diagnosis certain. As a rule, however, only the observation of an actual attack will settle the matter.

#### ÆTIOLOGY

Paroxysmal tachycardia may occur at any age. Cases have been recorded in children and in patients over seventy, but it is commoner in the middle period of life than at the extremes. My youngest patient was twenty, my oldest sixty-two; twelve patients were between twenty and forty, seven between forty and sixty, and one over sixty. The condition is commoner in men than in women; twelve of my patients were men and eight women. In Lewis' <sup>1</sup> series men were twice as numerous as women.

Paroxysmal tachycardia is usually found in association with some form of organic heart disease; five of my patients had mitral stenosis, six had myocardial degeneration, and two had myocarditis following influenza. It is not infrequent, however, to find no evidence of organic disease, and in seven of my patients the heart, when examined in the intervals between the attacks, appeared perfectly normal; in six of these cases there was a diminished exercise tolerance, but in one the patient was able to do anything he liked except when suffering from an attack.

The commonest immediate cause of an attack is some emotion; the excitement of a medical examination may promote one, and I have two patients, in whom simply feeling the pulse is sufficient to cause the heart to change its rhythm. I know one unfortunate man, with a keen sense of humour, who gets an attack whenever he hears what appeals to him as a really funny story; his immoderate laughter is only cut short by the discomfort he experiences when his pulse rate suddenly jumps to

180. Exercise may bring on an attack, and some patients ascribe the onset of the disease to some unwonted exertion. Sometimes a meal will be soon followed by an attack, and it is in these cases that it is so difficult from the history alone to judge whether the patient is suffering from true paroxysmal tachycardia or from palpitation due to flatulence.

#### TREATMENT

There is no infallible method of stopping an actual attack, but many different means may be tried, and frequently one of them is successful, although it is impossible to say which is likely to be the most efficacious in any particular case. The following methods should be tried.

(1) *Abdominal compression with a tight binder.*—Some patients have already found out for themselves the value of abdominal pressure, and can stop attacks themselves by leaning forward with the arms pressed firmly into the abdomen.

(2) *Local applications to the precordium.*—I have on four occasions seen attacks stop directly after a very hot fomentation has been applied to the chest, and even if this does not stop the attack, it greatly relieves the pain and discomfort. Lewis recommends the application of an icebag.

(3) *Drug treatment.*—Drugs likely to promote the cructation of flatus should always be tried, as this may stop an attack. Vomiting may have the same effect, and a case is recorded of a patient who always carried some ipecacuanha with him for use if an attack started. In view, however, of the possibility of sudden death during an attack, the induction of vomiting with its consequent effect on the circulation is not without danger. I have seen attacks terminate soon after an injection of strophanthin, and the same result has been found to follow the injection of digalen; morphia is much more effective than either, and I have been more successful with this than with any other of the methods of treatment advocated; it often stops the attack and, even if it does not, it enormously increases the patient's comfort. It is, moreover, a perfectly safe drug, except in cases where there is engorgement of the lungs. Other sedatives, such as chloral and bromide, have been used, but morphia on account of its more rapid action is preferable.

(4) *Pressure on the vagus.*—Stimulation of the vagus by firm pressure over the carotid sheath at the level of the thyroid will sometimes stop an attack. I have frequently tried this method, but have only been successful in one case; in this patient, a man suffering from effort syndrome, pressure for less than a couple of minutes was always effective.

In many cases, however, all means fail to influence the tachycardia, and in these all we can do is to get the patient into whatever position is most comfortable—most patients prefer to lie in bed, propped up with pillows—keep him quiet, if necessary with sedatives, and wait for the attack to terminate spontaneously. Although this is discouraging, I think that most writers are unduly pessimistic about our power to control attacks; when the same method is repeatedly successful in the same patient, we are surely wrong in ascribing it to mere coincidence, and a trial of the various means of treatment I have outlined is frequently effective. Should signs of cardiac failure, such as cyanosis and urgent dyspnoea, supervene during an attack, the best methods of treatment are venesection (10–15 ozs.) and the administration of oxygen; oxygen should be given through a mask, fitting closely over the face, or through a nasal catheter, to prevent too much mixing of the gas with air; it is necessary to give a much greater concentration of oxygen than is possible with the ordinary method of giving it through a funnel.

In the prevention of the attacks the first essential is to remove the cause; dyspepsia must be treated, excitement avoided as far as possible, and in cases where exertion brings on attacks, the patient's activities must be curtailed. A long course of digitalis in full doses may diminish their frequency, but the best results I have had have followed the administration of bromide.

During the war I saw the termination of a typical attack in a French civilian, the pulse rate dropping abruptly from 200 to 90; his attacks had started two years previously, and occurred on an average four times a week. Fifteen grains of potassium bromide three times a day kept him completely free from attacks for two months; he then stopped the bromide, and the attacks returned, but ceased again on resuming the bromide. He was able gradually to reduce the dose, and when I last heard of him only required five grains twice daily.

Another example of the value of bromide was afforded by the case of a pregnant woman, who was admitted into Guy's about a week before term. She had had influenza a few weeks before, and this had been followed by slight cardiac dilatation and attacks of palpitation; her description of these attacks was very suggestive of paroxysmal tachycardia, and soon after admission to hospital she had one which was quite typical. These attacks were completely stopped by bromides, labour was normal, and the attacks did not return during the following six weeks, while she was under observation. Bromides, however, do not always

have such good results, and in the case of a nurse the attacks persisted in spite of full doses, although their duration and frequency was diminished.

#### PROGNOSIS

Some idea as to prognosis has already been given in considering the question of treatment. In some cases this abolishes the attacks, in some they cease spontaneously after a few months or years, but in others they persist indefinitely. In cases where the attacks are unassociated with evidence of organic heart disease the danger to life is small, but they always cause some disability; the patient is usually completely incapacitated during an attack, and in the intervals, as has already been pointed out, his exercise tolerance is diminished. Of my seven patients, who were included in this group, five were capable of light work, one had no disability except during his attacks, and one died of bronchitis, complicating fibrosis of both lungs. In cases of organic heart disease paroxysmal tachycardia undoubtedly adds to the gravity of the outlook; six of my patients in this group died; three of them had had several attacks of cardiac failure, and the prognosis, apart from the paroxysmal tachycardia, was bad; in the other three, however, compensation was fairly well maintained, and the damage to the heart did not appear to be very grave; all three died in an attack of long duration, and it appeared that death was due to the inability of the heart to stand the tax thrown upon it by the continuous and persistent tachycardia. The other seven patients in this group have not shown the more serious signs of cardiac failure; most of them can walk fairly comfortably along the level, but cannot go uphill; one, a woman with mitral stenosis, however, is sufficiently well to play a little tennis. In all of them the attacks are infrequent and of short duration.

The prognosis of paroxysmal tachycardia as regards life may be summarised as follows: the outlook in cases where there is no evidence of organic heart disease is very good, but in cases where this is present, frequent and prolonged attacks greatly add to the gravity of the prognosis.

#### REFERENCES

- <sup>1</sup> T. Lewis: *Clinical Disorders of the Heart Beat*, Chap. V., 1911.
- <sup>2</sup> H. G. Butterfield and G. H. Hunt: *Quart. Journ. Med.*, vii, 209, 1914.

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NOTE.—The Chart labelled "A" in Dr. Cameron's paper in the January No. should have been labelled "B," and that labelled "B" should have been labelled "A."



# ANOMALIES OF SECRETION IN THE UPPER ALIMENTARY TRACT

## AN EPITOME OF RECENT INVESTIGATIONS

By T. IZOD BENNETT, M.D., Assistant Physician to the Middlesex Hospital and Beit Memorial Fellow for Medical Research

### PART I

#### A. INTRODUCTORY

At the period when J. A. Ryle and the present writer were engaged in examining a large series of normal men by the fractional method of gastric analysis, E. C. Dodds, working in the Bland-Sutton Institute of Pathology, Middlesex Hospital, published his original paper<sup>1</sup> showing that the taking of a

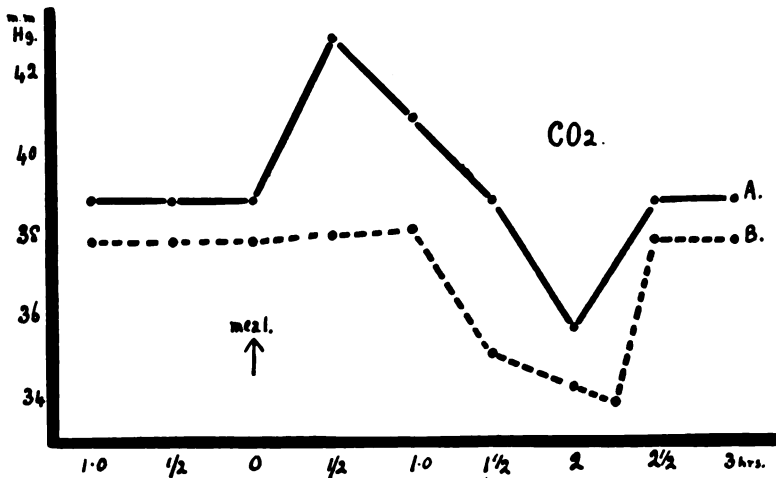


FIG. 1.

Variations in alveolar CO<sub>2</sub> tension after meals: (A) from a normal subject; (B) from a case where stomach had been excised.

meal produces a change in the tension of alveolar CO<sub>2</sub> in a normal subject at rest, the change being at first a rise of tension, which is followed by a fall below, and a subsequent return to the original level. Such a curve is shown in Fig. 1, which is reproduced from Dodds' original paper. He was at the same

time able to give the result of a similar examination of a patient whose stomach had been almost completely removed; in this case, as shown in Fig. 1, the rise of tension after a meal was not present, but the later fall took place normally. From these and kindred observations, Dodds deduced that the rise of  $\text{CO}_2$  tension, which follows the taking of a meal by a normal subject, was due to the secretion of acid by the stomach, and that the later fall probably represented alkaline secretion below the pylorus.

The fact that I had at my disposal a large number of medical students at the Middlesex and Guy's Hospital, who had voluntarily presented themselves for gastric analysis, provided an opportunity for testing the value of these two methods of estimating gastro-intestinal secretion; by examining the alveolar  $\text{CO}_2$  changes in a series of men known to have gastric secretion of very variable quantity and quality, we were able to establish the accuracy and utility of both methods, and it became apparent that we were in a position to study the abnormalities of secretion in the upper alimentary tract from rather a novel point of view.

Sufficient cases have now passed through our hands to enable us to make certain deductions, and it is my endeavour in this paper to describe our recent work, some of which has been published or communicated elsewhere. The conclusions which have been reached are in some instances at variance with existing views, and I am aware that our work cannot properly be regarded as more than preliminary, but our results have been consistent throughout, and have, I believe, a strong basis of experimental support.

## B. METHODS EMPLOYED

### 1. *Gastric Analysis*

The fractional method of gastric analysis has been employed in all this work; details of this procedure are familiar to readers of these Reports, and it is unnecessary here to say more than that great care has been devoted to two points—the complete removal of the fasting content before the test-meal is given, and the full removal in most cases of the total gastric content at the end of two and a half hours. These, I believe, to be very important details. It cannot be over-emphasised that the examination of small samples removed from the stomach only gives information as to the *concentration* of acid, etc. in the organ, which is a very different thing from the actual *amount* of such secretions. It is sometimes possible, for example, to obtain a few c.c. of juice from a rapidly emptying stomach,



in which the HCl reaches a very high degree of concentration, although there is not a vast amount of secretion being evolved; in other stomachs it is sometimes possible to show, by withdrawing the total gastric content two and a half hours after a meal, that a very large amount of juice has been secreted, though its concentration may not be greatly above the height of the normal average. Neglect of this conception has, I believe, been responsible for much false deduction in the past, and its importance will be more fully demonstrated in later sections of this paper.

The Boas test-meal of oatmeal gruel has been employed throughout these investigations.

## 2. *Alveolar CO<sub>2</sub> Estimation*

In this part of the work the subject is examined under conditions as closely analogous as possible to those employed for the direct gastric investigation. All subjects have been seen early in the morning, having had neither food nor drink since 10 p.m. on the previous night.

The fasting level of CO<sub>2</sub> tension is decided by examination of several specimens as soon as the subject has sat at rest for a sufficient time to secure repose. A test-meal, consisting of two rusks and a glass of milk, is then given, and samples of alveolar air are examined every subsequent fifteen or twenty minutes until the whole cycle of change is over. It would clearly be in some ways an advantage if the same test-meal could be used in both investigations, but we have felt that, in the absence of necessity for a readily aspirated and titrated meal, it would be unfair to the subject to deprive him of the more palatable and physiological meal which the CO<sub>2</sub> method allows.

The specimens of alveolar air were at first collected by the Haldane-Priestley method, the subject breathing into a long tube from which a projecting sideways allowed collection of the specimen into the Haldane gas-analysis apparatus. In later work it has been found that more accurate samples can be obtained by removing the sample direct from the subject's mouth by means of a "Record" syringe, the nozzle of which is then rapidly closed with the finger and inserted in the Haldane gas-analysis apparatus. The whole success of the CO<sub>2</sub> method depends upon the observer's accuracy and skill in the collection and analysis of the sample; no method such as the employment of exhausted receivers is sufficiently accurate for the collection of samples, and no apparatus that we have seen, other than that of Haldane, has sufficient accuracy for the estimation of CO<sub>2</sub> tension in the samples. Each observation of CO<sub>2</sub> tension

must be calculated from the mean of two samples—one, the “expiratory” sample, being taken on forcible expiration at the end of a normal expiration, the other, or “inspiratory” sample, being taken on forcible expiration at the end of a normal inspiration. The advantage of the syringe method of sampling lies in the ease with which it is applied in the case of nervous subjects, whose anxiety to help often prevents them from breathing normally into a large tube.

#### C. ACID AND ALKALI SECRETION AND THE HÆMATO-RESPIRATORY MECHANISM OF NEUTRALITY REGULATION

If by fractional gastric analysis it can be shown that a man secretes free HCl as the result of taking a test-meal, it will be found that contemporaneously with this secretion of acid there is a rise of alveolar  $\text{CO}_2$  tension; should his secretion of acid be great, the rise of  $\text{CO}_2$  tension will be correspondingly great; in exceptional cases, as will be shown later in this paper, the rise may be as much as 15 mm. of Hg, corresponding to a difference of nearly 2 per cent. in the  $\text{CO}_2$  content of his alveolar air.

Why should such a change occur in the alveolar air as the result of secretion by glands of the alimentary canal? The answer becomes clear as soon as it is realised that all the secretions of the digestive glands must be derived from the blood-stream. When one remembers that the stomach may secrete a pint or more of highly acid juice, and that this juice must be elaborated by the gastric glands at the expense of the blood which supplies them, it is evident that the procedure must tend to lower the H-ion concentration of the general blood-stream, or, in other words, to produce an alkalosis. Now it has come to be recognised by physiologists that the body will never readily suffer a change in the H-ion concentration of the blood, and that any change in such concentration will immediately affect the sensibility of the respiratory centre.  $\text{CO}_2$  is continually being evolved by tissue-metabolism and its discharge from the blood is ensured by the pulmonary ventilation; here then exists a method for maintaining the requisite constancy of the blood's H-ion concentration. A loss of acid into the stomach at once tends to lower the H-ion concentration, the lowered sensitiveness of the respiratory centre results in diminished pulmonary ventilation, the loss of the volatile acid  $\text{CO}_2$  via the pulmonary capillaries, alveolar air and expired air is diminished, the  $\text{CO}_2$  tension of the blood is increased to a degree sufficient to maintain the H-ion concentration at

its previous level, and this increase in blood  $\text{CO}_2$  tension is accurately reflected in the increase in alveolar  $\text{CO}_2$  tension.

This explanation appears to be the logical inference drawn from the available data, and I know of no serious criticism of it. Objection was at one time raised by observers, who had failed to find any alteration in the blood, such as one might expect in relation to such a mechanism; criticism loses weight in view of recent work by Dodds and McIntosh,<sup>3</sup> whose findings in a large series of blood-examinations I am able to reproduce in Table I. It will be seen on reference to this table that a number of subjects with normal secretion, and two men with achylia gastrica, were observed before a meal and at a later moment

TABLE I.

Subject No.	Alv. $\text{CO}_2$ tens.		$\text{CO}_2$ in plasma (Van Slyke's Mtd.).		P <sub>H</sub> of plasma (McClendon's Mtd.).		$\text{CO}_2$ in vols % (Haldane's method).					
							Whole blood.		Plasma.		Corpuscles.	
	Before.	After.	Before.	After.	Before.	After.	Before.	After.	Before.	After.	Before.	After.
1	40.23	44.30	64.20	64.20	a. 7.80 b. 7.40	7.82 7.40	58.5	67.0	27.5	27.0	30.0	39.1
2	42.35	47.74	64.20	64.20	a. 8.08 b. 7.40	8.13 7.50	57.0	66.5	28.5	28.5	27.5	37.0
3	41.91	48.01	68.70	68.70	a. 8.16 b. 7.40	8.20 7.42	54.5	63.0	35.6	35.7	19.3	27.0
4	41.04	44.80	65.39	65.40	a. ? b. 7.49	? 7.49	53.5	59.0	26.7	26.0	26.4	31.0
5	35.20	38.20	71.93	72.03	a. 8.25 b. 7.48	8.30 7.55	54.0	61.5	26.5	27.0	28.5	34.0
6	37.34	43.81	72.10	72.94	a. 7.90 b. 7.42	7.90 7.64	49.0	59.0	25.0	25.0	26.0	34.0
7	35.21	40.20	68.32	68.50	a. 7.80 b. 7.40	7.90 7.50	48.1	56.0	24.1	24.0	23.9	31.0
8	35.96	35.57	62.10	62.10	a. ? b. 7.40	? 7.40	48.2	48.6	25.5	25.6	23.1	22.9
(Achyilia) 9	36.10	36.20	68.40	68.40	a. 7.90 b. 7.40	7.95 7.40	49.0	49.5	24.0	24.1	24.3	24.9
(Achyilia)												

during the height of gastric secretion. The readings marked "before" indicate the first, those marked "after" the second observation in each case. The alveolar  $\text{CO}_2$  tension, except in the case of the subjects with achylia, shows the typical rise, the alkali reserve shows no change, nor does the  $\text{P}_{\text{H}}$  of the plasma. When, however, the  $\text{CO}_2$  tension of the blood was examined, a very different picture is given, the whole blood (again except in the case of subjects with achylia) shows a very definite rise, and when plasma and corpuscles were examined separately it appeared that this rise had occurred almost exclusively in the corpuscular portion of the blood. The explanation of previous failures to demonstrate this is probably either that the observer examined plasma rather than whole

blood, or else that the specimens were not examined rapidly enough after withdrawal, a very short interval being sufficient to produce hopelessly confusing changes.

#### D. THE SIGNIFICANCE OF THE FALL IN $\text{CO}_2$ TENSION AT A LATER PERIOD OF DIGESTION

The fact that the rise of  $\text{CO}_2$  tension varied directly with the degree of gastric secretion suggested that the later fall in tension must correspond to the degree of alkali secreted into the duodenum. The fact that this fall without any preceding rise was well marked in subjects whose only known abnormality was an absence of gastric secretion further supported this view. More evidence on this point was clearly desirable, and with a view to obtaining it, a series of experiments was devised by which food was introduced directly into the duodenum. One

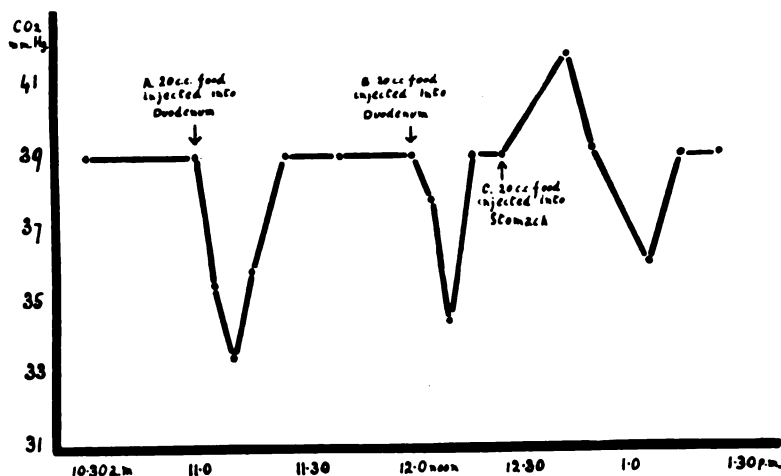


FIG. 2.

Variations in alveolar  $\text{CO}_2$  tension produced by the direct introduction of food into the duodenum (A and B) and stomach (C).

of these experiments, which will be found fully described elsewhere,<sup>4</sup> is reproduced in Fig. 2. The subject, fasting, swallowed an Einhorn tube to a depth sufficient to allow of its traversing the pylorus; at the end of about an hour, alkaline bile-stained fluid was aspirated, indicating that the end of the tube was now in the duodenum. The fasting level of alveolar  $\text{CO}_2$  tension having been ascertained, 20 c.c. of gruel were introduced directly through the tube, and it was found that a typical fall in tension was produced (Fig. 2, A.). This was later repeated at the point B; the tube was then withdrawn until its end was in the stomach.

Introduction of food now produced a typical gastric rise of  $\text{CO}_2$  tension with the later fall as usual (Fig. 2, C.).

From this series of experiments it becomes clear that the fall in  $\text{CO}_2$  tension during later stages after a meal does correspond with the entrance of food into the duodenum; and knowing that the previous rise is directly associated with the loss of gastric HCl from the blood-stream, there appears to be no escape from the conclusion that the fall must represent secretion of alkali. Much previous work, and particularly that of Boldireff,<sup>5</sup> has established that the source of alkali in the duodenum is threefold, coming from the pancreatic juice, the bile, and the glands of the intestine. It has furthermore established that the pancreatic juice is the predominant factor. It may, I believe, be accepted that any definite fall in a subject's  $\text{CO}_2$  tension occurring as the result of a meal represents his secretion of alkaline pancreatic juice.

#### E. THE CONTINUOUS NATURE OF GASTRIC AND PANCREATIC SECRETION AND THE EFFECTS OF ATROPINE ON SUCH SECRETIONS

It is a fact familiar to all that the secretion of the salivary glands is continuous; reaching its maximum during the mastication of savoury food, it still continues between meals. The observations of Carlson,<sup>6</sup> made upon a subject with œsophageal stenosis and a permanent gastric fistula, have established that in ordinary life the stomach also secretes slowly and continuously even when empty. Starvation appears to arrest this in time, but normally there is a perpetual slight evolution of acid juice between meals.

I have formed the opinion that the pancreas must also be considered as a continuously secreting organ, producing small amounts of alkaline juice even when the duodenum is empty, and secreting in far greater degree in response to stimuli, the exact nature of which can only be surmised, but which reach it whenever food enters the duodenum.

This was the conclusion which Dodds and I arrived at as the results of our experiments with atropine; details of these have been published elsewhere,<sup>4</sup> but they may be summarised as follows.

1. Gastric lavage with a weak solution of atropine arrests the secretion of HCl.
2. The introduction of food into a stomach, which has been washed with a weak solution of atropine, is not followed by the rise of alveolar  $\text{CO}_2$  tension which normally occurs, but the

fall in tension which occurs later, when the food has traversed the pylorus, is not interfered with.

8. If the duodenum be washed with a weak solution of atropine by means of a tube which traverses the stomach leaving that organ untouched, the normal fall of  $\text{CO}_2$  tension, which occurs whenever food reaches the duodenum, is arrested. The rise of  $\text{CO}_2$  tension, corresponding to a secretion of acid, can still be produced by introduction of food into the stomach.

These facts can be seen demonstrated in Figs. 3 and 4, which show the readings of  $\text{CO}_2$  tension obtained in healthy subjects investigated in the manner indicated.

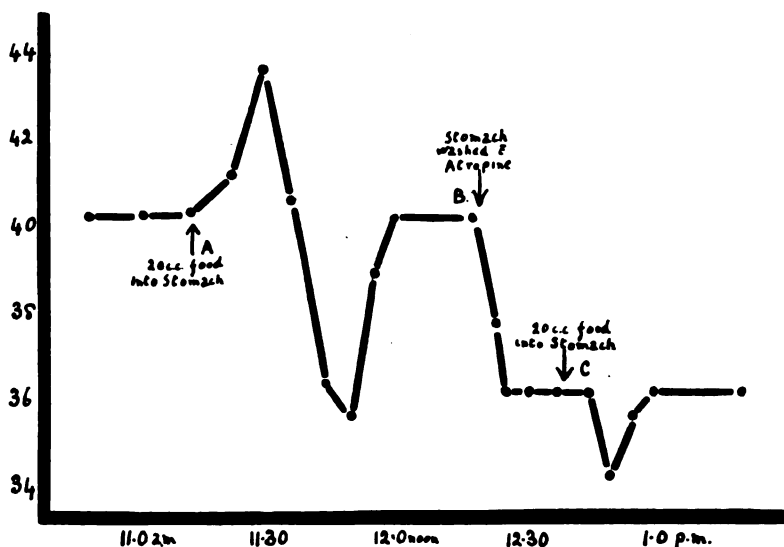


FIG. 3.

Variations in alveolar  $\text{CO}_2$  tension produced by the introduction of food into the stomach before and after gastric lavage with a solution of atropine.]

But the experiments, in addition to demonstrating the power of local atropine applications of arresting the normal acid and alkali secretions in response to food, bring out something less easily foreseen. It will be observed on reference to Fig. 3 that gastric lavage with atropine was immediately followed by a fall in the fasting level of the  $\text{CO}_2$ , and that the fasting level remained in this new position until the end of the experiment; conversely Fig. 4 demonstrates that duodenal lavage with atropine causes an immediate rise in the fasting level to a new position, which is maintained. What is the explanation of these phenomena? They can, I believe, be explained in only one way—that a continuous secretion either of acid or of

alkali has been suspended by the action of the drug. The result of these experiments was unexpected, but the conception is not a surprising one on review; knowing the continuous nature of salivary and gastric secretion, and indeed of active glands in general, there is nothing peculiar in the pancreas also being a continuously secreting organ.

Very suggestive is the light which this conception sheds on the significance of the fasting-level of alveolar  $\text{CO}_2$  tension;

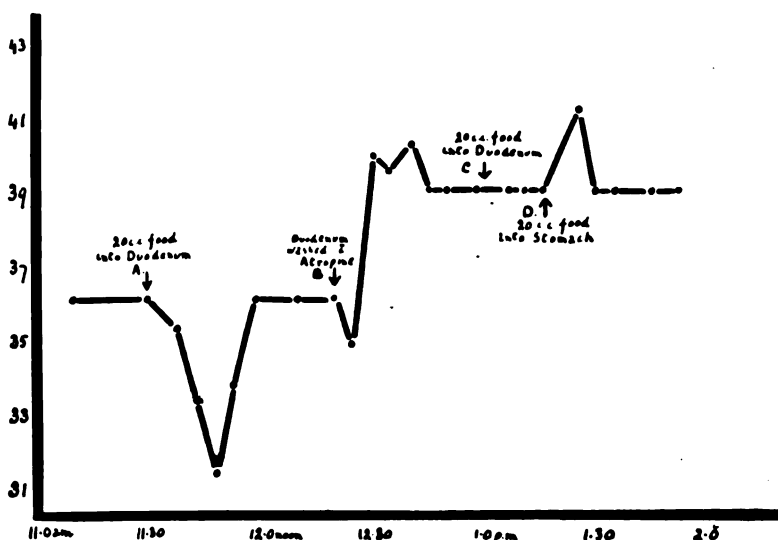


FIG. 4.

Variations in alveolar  $\text{CO}_2$  tension produced by the introduction of food into duodenum or stomach before and after duodenal lavage with atropine.

for the change in this level, which follows the arrest of a continuous secretion, shows that the normal level must be looked upon as a point of balance between a continuous loss of acid by the stomach and a continuous loss of alkali by the pancreas. It will be seen in a later portion of this paper that subjects with gastric hypersecretion do show a high fasting level of  $\text{CO}_2$  tension, and that another class, whom we believe to have pancreatic hypersecretion, show an unusually low fasting level.

#### F. THE NORMAL AVERAGE CONTROL PICTURE

For purpose of comparison with abnormal cases, it is necessary to reproduce the figures indicative of the normal. This I have done in Fig. 5. The black ribbon, which shows the normal average HCl given by fractional gastric analysis, is derived from the work by J. A. Ryle and myself.<sup>7</sup> For  $\text{CO}_2$  tension figures it is impossible to make any such general tracing, because

the variation in the fasting level in individuals is too great; the four curves reproduced may be accepted as representative of the usual picture in health; that is to say, the average man

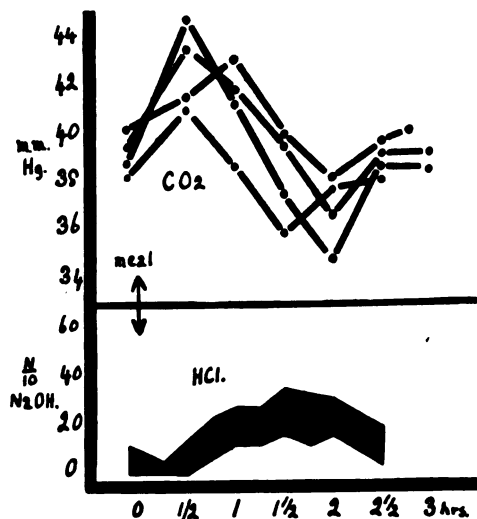


FIG. 5.

The response of normal men to test-meals. Above are four typical curves of alveolar CO<sub>2</sub> tension. Below the tracing of free HCl in gastric contents of the great majority.

is found to have a rise of 3-5 mm. Hg. in response to a meal, with a drop of corresponding depth at later stages.

The variations from these figures encountered in health will be found fully described elsewhere.<sup>2, 7</sup>

## PART II

### A. HYPERSECRETORY STATES

#### 1. Gastric Hypersecretion ; *Reichmann's Syndrome*

A general survey of the literature concerning gastric hypersecretion will, I believe, convince any reader that in all countries there exists a baffling state of confusion regarding the subject. This is very largely due to the fact that it has become customary to label as "hyperchlorhydria" or "hypersecretion" any case in which the gastric contents have been shown to contain a high concentration of HCl.

Recent investigations have tended to confirm Pavlov's view that the gastric secretion does not change from moment to moment as regards its acid strength, though the rate of secretion is capable of wide variation; and one feels that the word



hyperchlorhydria is one which should be avoided in medical literature, unless more precision can be arrived at regarding its definition. On the other hand, the term hypersecretion has been almost equally abused. Since the advent of fractional gastric analysis both English and American writers usually refer to any constantly rising curve of acid concentration as "hypersecretory"; careful study of the factors responsible for such a curve makes clear the error in such reasoning.

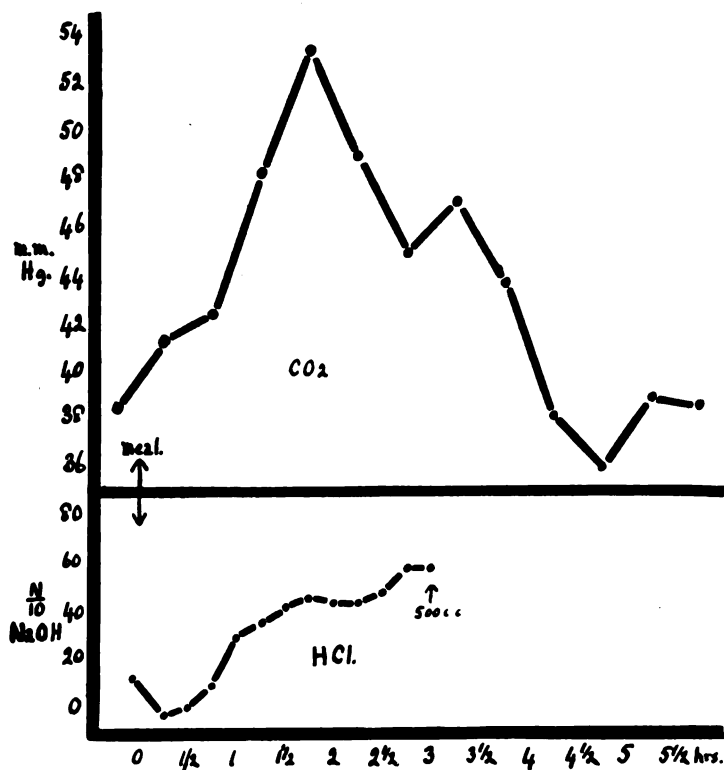


FIG. 6.

Curves of alveolar CO<sub>2</sub> tension and of free HCl in gastric contents from a subject with marked *concentration* of gastric acidity but without very marked hypersecretion.

In Figs. 6 and 7 will be seen curves of gastric HCl from two subjects; each rises steadily, one to the extreme titre of 104  $\frac{N}{10}$  NaOH, the other to a less extreme figure. Yet the case with the highly concentrated gastric contents had little juice in the fasting stomach, and from one and a quarter hours after the test-meal it was with difficulty that sufficient could be aspirated from the stomach for purposes of analysis. In

the case with the less concentrated contents there was abundant resting-juice, well over 100 c.c., and at two and a half hours over 300 c.c. of gastric contents, containing very little of the starchy meal, were recovered. Clearly it is in the latter case that true hypersecretion existed, and the  $\text{CO}_2$  curves from these cases demonstrate that fact very dramatically. For in the first case (Fig. 6) there is a rise of 7.5 mm. of Hg. only, whereas the second gives a rise of no less than 15 mm.; comparison with the normal average figures shows the extent of this change.

Until the alveolar  $\text{CO}_2$  estimations had been performed on

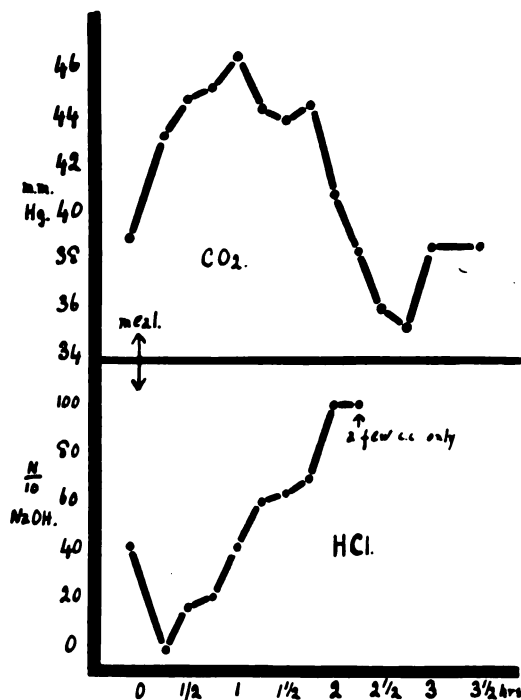


FIG. 7.

From a case of true gastric hypersecretion.

these cases I had personally overlooked the distinction between them, believing indeed that the case with extreme concentration was also the one with the greater total secretion of gastric juice. Re-examining them it became clear that the reverse was true; the subject illustrated in Fig. 6 had a fasting content of high titre, but small in amount, and the difficulty of recovering anything from his stomach after one and a quarter hours was a notable feature; the subject in Fig. 7 was proved, by the recovery after two and a half hours of 300 c.c., containing very little starch, to have a true hypersecretion. It is only by care-

fully looking for such evidence that cases of hypersecretion can be identified, mere high acidity alone being insufficient.

In 1882 Reichmann,<sup>8</sup> a Polish physician, published his first account of gastrosuccorrhœa, a disease or syndrome said to be characterised by headache, vomiting of excessive acid juice, and other rather indefinite symptoms. His work has not been fully accepted, and, following largely upon the criticisms of Soupault,<sup>9</sup> the French school of gastro-enterologists have in general denied it, laying down that hypersecretion is always an accompaniment of an organic lesion in or near the alimentary tract, or even that every case of ulceration near the pylorus is accompanied by hypersecretion.

Our recent observations do not support this latter view; we have only encountered a condition that could clearly be called gastric hypersecretion in five cases. Two of these were men apparently in good health, with no sign or symptom of disease. The third had trivial symptoms and would certainly not have called for serious investigation in the course of usual medical routine; he was a medical student, who volunteered the opinion that his condition was a neurosis; certainly his symptoms have disappeared after a few weeks' treatment with atropine and regulation of his mode of life. Of the remaining two one had symptoms very suggestive of duodenal ulcer, and the last was found at operation to have a very large ulcer of the duodenum.

Eliminating all cases in which pyloric obstruction or spasm causes prolonged food-retention and hence prolonged gastric stimulation, there is certainly a class of case in which gastric hypersecretion is a very real phenomenon; that any disease is present I have no evidence, but the condition is a definite one, and is to my mind of particular interest in view of the section of this paper which immediately follows.

## 2. *Pancreatic Hypersecretion ; Diabetes Mellitus*

The extreme degree of gastric secretion seen in the group of cases just described raised the question as to whether an analogous condition might not sometimes exist in the pancreas. I have referred to the significance of the fasting level of CO<sub>2</sub> tension as a balance between gastric and pancreatic secretion, a high level being indicative of increased secretion by the stomach. It is equally well established that low or absent gastric secretion is associated with a low fasting level of CO<sub>2</sub> tension; if cases of pancreatic hypersecretion occur they too should be characterised by a low CO<sub>2</sub> level.

Such were the considerations which directed our attention

to diabetes mellitus, for since the valuable work of Beddard, Pembrey and Spriggs,<sup>10</sup> who first described the application of alveolar air analysis to the problem of diabetic coma, it has been established that severe diabetes is frequently associated with a very low alveolar  $\text{CO}_2$  tension.

It is usually believed that such lowering of  $\text{CO}_2$  tension in diabetes is the result of ketosis; acetone bodies, the product of deficient fat katabolism, being present in the blood and replacing a certain amount of the normal  $\text{CO}_2$ ; supporting this view is the well-established fact that the lowest recorded readings of  $\text{CO}_2$  tension occur when the patient is on the verge of coma,

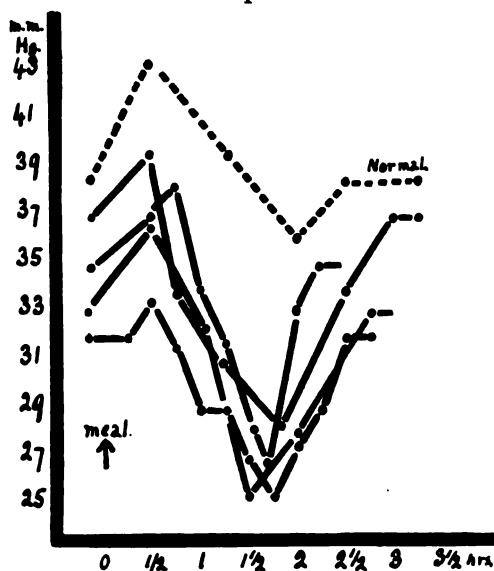


FIG. 8.

Curves of alveolar  $\text{CO}_2$  tension following test-meals, in a series of cases of diabetes mellitus; to illustrate exaggeration of pancreatic fall.

with marked ketonuria. With this observation we fully concur, but in addition we have observed that even in the absence of evidence of ketosis it is usual to find a low  $\text{CO}_2$  tension in marked cases of diabetes.

A full account of our first observations will be found elsewhere;<sup>11</sup> we have now had the opportunity of examining more than twelve cases of severe diabetes, and representative curves of  $\text{CO}_2$  tension from a series of these are shown in Fig. 8. It will be seen that the fasting level of  $\text{CO}_2$  tension is low, and that in addition there is in response to the test-meal a fall in tension much greater than that seen in normal persons. We believe that this indicates a pancreatic hypersecretion, analogous to the gastric hypersecretion described in the preceding section,

and I feel that such a conception elucidates many obscure problems connected with diabetes.

It is, for instance, well known that the ingestion of more than 100 grammes of glucose will produce hyperglycæmia and glycosuria in most normal men, whereas 300 grammes of cane-sugar will produce no such effect. Suppose, however, that the 300 grammes of cane-sugar or even a starch meal were rapidly attacked by large quantities of pancreatic juice, clearly there would be a rapid production of excessive amounts of glucose in the small intestine, hyperglycæmia and glycosuria. If, on the other hand, the matter be considered from the point of view of the internal secretion of the pancreas, one's first thoughts are concerned with the difficulty of harmonising the small amount of pancreatic tissue left in the animal with experimental diabetes, and the apparently large amount of gland substance seen in the victims of severe human diabetes. Here again it would seem natural that in a human pancreas, which was pouring out excessive amounts of external digestive juice, there should soon occur an exhaustion of the islets of Langerhans and a deficiency of internal secretion. The whole conception seems to fit in with the known facts and the effects of the modern system of treatment to a surprising degree.

I am at present carrying out experimental work with a view to obtaining further information on these points; meanwhile it must be noted that these curves of  $\text{CO}_2$  tension, seen in diabetes, have been encountered in no other condition either physiological or pathological.

## B. HYPOSECRETORY STATES

### 1. *Gastric Hyposecretion*

I find it exceedingly difficult, when reviewing my personal observations, to make any general statement concerning achlorhydria, or benign achylia gastrica. One clearly important fact is the frequency of its occurrence in health. In the series of one hundred normal healthy men examined by Ryle and myself it occurred in four subjects; three other men in whom it was present were excluded from the series, although without sign or symptom of disease, on account of a past history of gastro-intestinal or general disorders.

No other real series of normals has, as far as I have been able to ascertain, ever been published; smaller series have been derived from patients with symptoms, but no signs, of organic disease, and the absence of achylia gastrica in such series points, I fancy, to the observers having accepted achlorhydria as a definite pathological sign.

The occurrence of complete achlorhydria in men, who are clearly in robust health, must make one pause before accepting it as necessarily a morbid condition; I have many times encountered it in patients with dyspeptic symptoms, but the majority of them have given no evidence of any definite disease. Usually their symptoms have appeared to be largely neurotic, slight discomfort and flatulence exaggerated by a hypersensitive individual.

My experience is that it is very rare to encounter a patient with benign achylia, whose stomach does not empty with marked rapidity, an effect which is in accordance with the conception of the acid control of the pylorus. A frequently empty stomach of this type will probably entail an unusual frequency of the hunger contractions which govern appetite, and it may well be that therein lies the explanation of the abnormal sensations

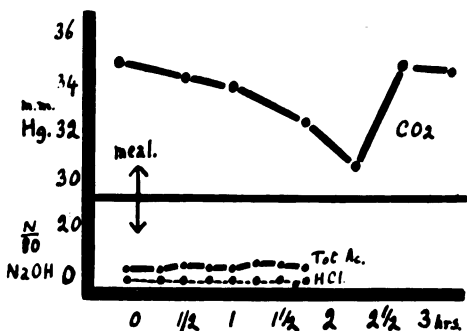


FIG. 9.

From a case of benign achylia gastrica.



FIG. 10.

Curve of alveolar CO<sub>2</sub> tension from a case of pancreatic insufficiency.

of this class of dyspeptics, as well as of the aerophagy which produces their flatulence.

In Fig. 9 are given the curves of gastric acidity and CO<sub>2</sub> tension from a typical benign achylia; the absent HCl and very low total acid are typical; the absence of gastric rise in CO<sub>2</sub> tension is well demonstrated, and the pancreatic drop is of normal depth, as would be expected in such a case, which shows no signs of pancreatic deficiency.

## 2. Pancreatic Hyposecretion

We have observed some six cases of pancreatitis, but only one of them was in sufficiently good health to allow of accurate data being collected. The patient, a man of forty, had for years had signs of pancreatic insufficiency, with unsplit fat and meat fibres in his fæces; a laparotomy was performed three years ago, revealing a fibrotic condition of the pancreas.

His CO<sub>2</sub> tension is shown in Fig. 10. The gastric rise is

less than usual; the pancreatic fall is so slight as to approach the limit of experimental error. I reproduce this because the case was one in which the diagnosis was confirmed and because the patient was in sufficiently good general health to permit accurate observation.

### 3. *Gastro-Pancreatic Hyposecretion. Addison's (Pernicious) Anæmia*

The association of pernicious anæmia with diminished gastric secretion has been recognised since the pioneer observations of Samuel Fenwick.<sup>12</sup> Authorities differ as to the exact frequency of complete achlorhydria in this disease, but it is unquestionably present in the majority of cases even at the first examination that is made. Using the old single-estimation method of gastric analysis Cabot<sup>13</sup> reports but one case in 79 with any marked secretion of HCl; Friedenwald and Morrison<sup>14</sup> found 42 cases of complete achlorhydria in a series of 57, and, more recently Levine and Ladd,<sup>15</sup> using a Rehfuß tube and examining specimens at intervals after meals, found achlorhydria in all but one of 105 cases.

It must be conceded that in none of these series have the technique of gastric analysis or the clinical criteria for making the diagnosis been such as to eliminate all error, but it would seem that the greater the attention that is paid to such details the higher becomes the proportion of cases of Addison's anæmia in whom there is complete achlorhydria.

In the last number of these Reports prominence was given to the problem of the etiological significance of this factor, Dr. A. F. Hurst in particular being emphatic in support of the thesis that the anæmia is probably the result of an infection which reaches the blood-stream owing to a previous loss of the protective gastric HCl.

Observation of the alveolar CO<sub>2</sub> tension of cases of Addison's anæmia throws an additional light on the question. This will be appreciated by referring to the upper part of Fig. 11, where will be seen the CO<sub>2</sub> tensions from four typical cases. The contrast which these present with benign cases such as are illustrated in Fig. 9, lies in the fact that in Addison's anæmia there is a marked diminution in the pancreatic drop as well as in the gastric rise. This picture we have obtained in each of the six cases of Addison's anæmia which we have been able to examine by the double method. It will be observed that the gastric analysis, seen in the lower portion of the same figure, is in no way different from the picture given by benign cases (Fig. 9).

It seems certain, in view of these peculiar curves of  $\text{CO}_2$  tension, that in Addison's anæmia there is a diminished secretion from the pancreas as well as from the stomach; the supposition harmonises with the clinical experience that diarrhœa is a not infrequent symptom. It should, I believe, be accepted that diarrhœa occurring in association with a gastric hyposecretion is frequently due to pancreatic disorder; we know that many cases, probably the great majority, of benign achlorhydria have normal stools, we know that the absence of  $\text{HCl}$  in the gastric juice is a potential cause of infection lower down the bowel, and I find it difficult to believe that apart from some additional factor such as pancreatic deficiency, achlorhydria can produce diarrhœa.

Reverting to the peculiar curves of alveolar  $\text{CO}_2$  tension in Addison's anæmia, is it perhaps possible that they and the

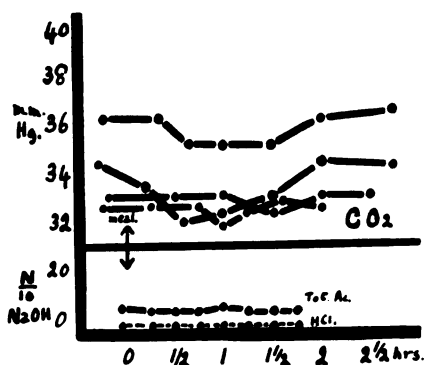


FIG. 11.

From a series of cases of pernicious anæmia, to show the marked diminution of pancreatic, as well as of gastric, response seen in this condition.

secretory disturbances are both secondary to the blood-condition? If for any reason the blood be materially altered it is clearly possible that the secretory glands may be unable to form from it the juices which they usually elaborate; the fact that there is evidence of hyposecretion both of the pancreas and of the stomach seems at first sight to be in accordance with such a view. Further, we have, in a very severe case of secondary anæmia, which followed months of uterine hæmorrhage, found complete achlorhydria, and a curve of alveolar  $\text{CO}_2$  tension with gastric rise and pancreatic fall much smaller in degree than the normal.

If it be true that achlorhydria precedes the onset of Addison's anæmia by months or years, it is probable that the blood condition does result from the loss of the stomach's normal bactericidal function; if, on the other hand, it be a fact that



cases of Addison's anæmia seen sufficiently early have a good secretion of HCl, it becomes more probable that the secretory disturbances are themselves hæmatogenous in origin.

In this connection I feel that we should not lose sight of the close resemblance which cases of Addison's anæmia bear to certain rather unusual cases of cancer of the stomach. Every clinician has occasionally encountered patients whose lemon-yellow complexion, weakness, breathlessness, wasting and vague digestive symptoms, without a typical blood-picture, and without a palpable tumour, render the differential diagnosis almost impossible. In my experience it is not uncommon in such patients to obtain a result on fractional gastric analysis which is typical of either benign achlorhydria or of Addison's anæmia, and yet the diagnosis has ultimately turned out to be carcinoma of the stomach.

It is interesting to remember that Samuel Fenwick, the physician who in England first discovered the secretory abnormalities of Addison's anæmia, was occupied by this very problem.<sup>16</sup> Seeking for some general causative factor in cancer, he examined the gastric mucosa of many patients who had died in the Cancer Charity of the Middlesex Hospital, and found atrophy of the gastric tubules in a large proportion of them, even when the site of the tumour was far removed from the stomach. Later <sup>12</sup> he made a similar investigation in cases of Addison's anæmia with even more definite results. His view was that in cancer and in Addison's anæmia there was a primary atrophy of the gastric glands which led to a disturbance of that digestive function of the stomach which was "necessary to enable the albuminous portion of the food to reach the vascular system." This theory is not far removed from the more modern one, which supposes that reduced bactericidal power of the stomach gives unknown toxins access to the blood.

Until further evidence has been collected from very early cases of Addison's anæmia one can but speculate as to the rôle played by the gastric hyposecretion. For the moment my purpose is to draw attention to the observations we have made, pointing to the presence of a pancreatic deficiency in this disease.

### C. SECRETORY DISTURBANCES CHIEFLY DEPENDENT UPON DERANGEMENT OF PYLORIC FUNCTION

#### 1. *Juxta-Pyloric Ulcer*

The number of cases of peptic ulcer which give laboratory findings that are of great diagnostic value has certain limitations; in my experience such cases are limited to those in which the

ulcer is juxta-pyloric in situation. A representative observation from a case of this class is given in Fig. 12; the diagnosis was confirmed by operation.

It will be seen that the HCl follows the climbing course of increasing concentration; the CO<sub>2</sub> curve shows a degree of secretion only slightly greater than that of the usual normal. This and a series of similar observations have convinced me that the usual findings in cases of gastric ulcer are indicative merely of a disturbance of the normal pyloric function. For it must again be emphasised that a climbing curve of HCl does not necessarily imply hypersecretion, it merely shows that the

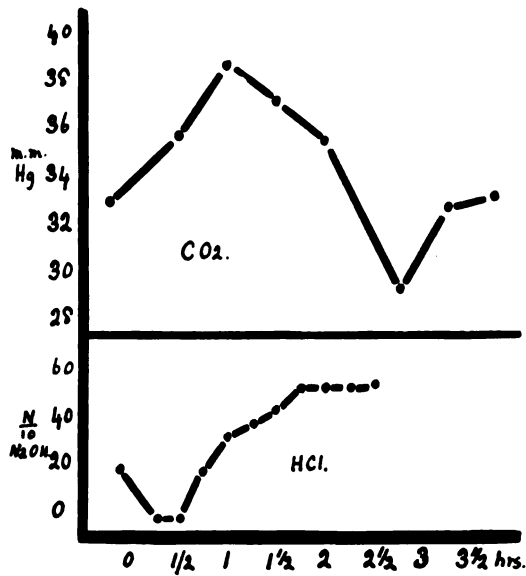


FIG. 12.

From a case of juxta-pyloric ulcer.

acid-production is continuously equal to or greater than the neutralising factors; the great neutralising factor, as Bolton and Goodhart have recently established,<sup>17</sup> is the regurgitation of alkaline pancreatic juice, and should its reflux be prevented by pyloric stenosis or pylorospasm, a climbing curve must result in any acid-secreting stomach. One knows that this type of curve may be met with in

- (1) a few apparently normal men;
- (2) dyspeptics with marked gastric hypersecretion;
- (3) many cases of gall-stones or cholecystitis;
- (4) many cases of tabes with gastric crises; and
- (5) certain cases of gastric or duodenal ulcer.

With the exception of the rare cases of true excess of secretion, I would suggest that in all these examples it is pyloric relaxation that is adversely affected.

Everyone who has investigated cases of gastric ulcer knows the infrequency of such a picture, and the anomalous nature of the symptoms, in cases where the ulcer is high on the lesser curvature, or far removed from the pylorus; our failures with such cases make it clear that none of us can dogmatise as to the diagnosis of ulcer by laboratory methods, they also suggest that it is the pyloric factor which usually is responsible for our successes.

## 2. *Juxta-Pyloric Cancer*

A typical picture from a case of cancer of the pyloric end of the stomach is reproduced in Fig. 13. The gastric analysis illustrates the almost absent HCl, the high total acid, and the delayed emptying characteristic of this condition. The  $\text{CO}_2$

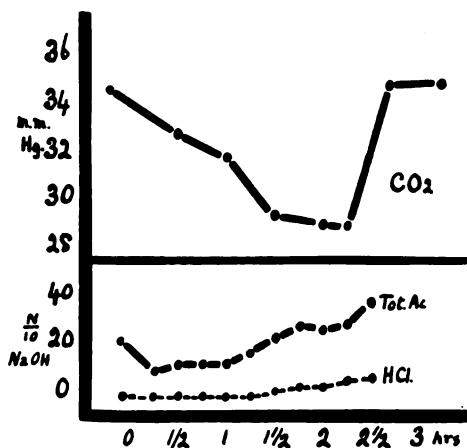


FIG. 13.

From a case of carcinoma of the pyloric end of the stomach.

curve shows an absence of the gastric rise, a normal pancreatic fall, and a delay in the whole secreting cycle. I believe that these, and all other approved tests for gastric carcinoma, are in reality merely tests for extreme pyloric stenosis, or for the decomposition of stagnant gastric contents.

I have succeeded in many cases in demonstrating a free secretion of HCl in such stomachs after washing the mucosa very carefully for some time; by the same means the total acidity can be reduced to normal limits, it being merely indicative of fermentation above an obstruction; the Opler-Boas bacillus, the lactic acid, the high mineral chlorides seen in such

cases, all I believe to be of similar origin; they are not seen in non-obstructive cases, they disappear with careful lavage. Two cases of gastric syphilis, producing similar pyloric blockage, have given me a precisely similar picture on gastric analysis.

Unfortunately this is not the only type of gastric carcinoma, and many cases, which do not block the pylorus, produce pictures far more difficult to interpret.

Amongst these are cases with achylia of possibly hæmatogenous origin, others with a secretion in no way differing from the normal, others with an abundant secretion of mucus, and others whose sole abnormality is gastric hurry produced apparently by mechanical stimulation by a tumour lying in the fundus of the stomach.

Diagnosis in such cases is frequently extremely difficult, and I have found that the most useful guide is usually the character of the resting-juice. Very frequently traces of altered blood, or of decomposing food remnants, can be demonstrated in this, whereas later fractions provide nothing of diagnostic significance.

I hope to deal further with these problems at a later date.

I would express my thanks to all my colleagues on the staff of the Middlesex Hospital and its Medical School for the facilities they have given me for making these observations; and especially to Dr. E. C. Dodds and Professor James McIntosh for permission to reproduce certain observations for which they are solely responsible. The greater part of the work here described has been performed by myself and Dr. Dodds in the closest collaboration, in the Bland-Sutton Institute of Pathology, and the Department of Physiology, Middlesex Hospital.

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## ADDISON'S ANÆMIA

### A STUDY OF SEVENTY-FIVE CASES, WITH SOME REMARKS ON THE PATHOLOGY

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PERNICIOUS, or, as we prefer to call it, Addison's anæmia is peculiarly associated with Guy's Hospital. It was originally described by Addison in 1855,<sup>1</sup> and from that time until 1909 all cases in the Hospital have been recorded in the *Guy's Hospital Reports* by Wilks,<sup>2</sup> Taylor,<sup>3</sup> Pyc-Smith,<sup>4</sup> Hale-White<sup>5</sup> and French.<sup>6</sup>

The present paper is an attempt to complete this series by analysing the cases which have been diagnosed as Addison's anæmia from 1909 until March 1922. As many cases as possible have been followed up after their discharge from hospital, to determine if the prognosis is really as bad as the old name of the disease would imply.

The information about the majority of the cases is derived from the clinical case sheets. Fortunately the value of the latter is enhanced by the fact that blood counts have been done not only by the ward clerks, but by Dr. Price Jones, Mr. P. P. Laidlaw, Dr. G. W. Nicholson and Dr. Bowell. On the whole the information given in the case reports as to history and symptoms has been satisfactory, as the disease has traditionally been regarded in Guy's Hospital as of special interest. A few cases, where the notes were too inadequate to be of any value, have been omitted from our figures. Most of the patients in hospital during the last two years of this series have been seen by one or both of the writers.

In dealing with any disease such as Addison's anæmia, in which the pathology is a matter of dispute, and the diagnosis cannot be determined definitely by laboratory or even post-mortem findings, it is naturally difficult to decide on what principles to include cases as genuine examples of the disease. In this paper we have included all cases which were diagnosed definitely by the physician in charge as Addison's anæmia, unless subsequent findings have proved them to be certainly some other disease.

Brief details of the present series are given in Appendix A. Tables I., II. and III. consist of definite cases of Addison's anæmia. Table IV. records cases of anæmia in which there is some doubt as to the diagnosis, and Table V. cases which are certainly not Addison's anæmia, but are interesting for comparison. In Appendix B are given fuller details of cases illustrating special points.

The cases included in Appendix A as definite cases of the disease are seventy-five in number. As the period covered is just over fourteen years, the average number per annum is 5.4. In French's series<sup>3</sup> he found sixty-eight cases in Guy's Hospital during the eighteen years from 1891 to 1908, the average number per annum being 3.8. If we go back still further we find that from 1855 to 1889 Hale-White was only able to find records of thirty-one cases, which gives an average of little over one case a year. It does not necessarily follow that the disease is more common than it was formerly. As Osler suggests, it is probable that practitioners are more alert than in the past, and the disease is better known. Moreover, statistics in any particular hospital are obviously misleading, as cases tend to be sent to hospitals such as Guy's, where the disease is regarded with special interest.

No attempt is made to analyse the present series with regard to the symptoms which are common in anæmia due to any cause. Such symptoms as œdema of the ankles, muscular weakness, dyspnœa on exertion, headaches and palpitation, were present in nearly all the cases and will not be further discussed. Similarly hæmic bruits were present in most cases and are not of any real significance in Addison's anæmia.

We propose, therefore, to discuss in detail only certain symptoms and signs which are characteristic of the disease, or which may throw some light on its pathology. The particular features to which special attention is directed are as follows :

1. Age and sex incidence.
2. Colour of skin.
3. Gastro-intestinal symptoms, including achlorhydria and lesions of the tongue.
4. Neurological symptoms.
5. Blood pressure and pigmentation.
6. Duration of the disease and remissions.
7. The changes in the blood.
8. The pathology of the disease.
9. Treatment.

*Age and Sex Incidence*

The sex incidence of the present series is compared in Table I. with that in French's cases,<sup>6</sup> with Levine and Ladd's American series,<sup>30</sup> and with Cabot's<sup>29</sup> very large series of cases.

TABLE I.

	Total number of cases.	Percentage males.	Percentage females.
Present Guy's series. . . .	75	60	40
Guy's cases 1891-1908 . . .	68	54	46
Levine and Ladd (Boston) . .	143	41	59
Cabot's series (collected cases) .	1157	62	38

It will be noted that our figures as to sex incidence agree very closely with the far larger series of Cabot, and are in marked contrast to the figures quoted by Levine and Ladd. Their cases in which an autopsy was performed show a percentage of fifty-five males to forty-five females, which suggests that they may have included among the non-fatal cases types of anæmia which would not be diagnosed here as Addison's anæmia.

As regards age incidence the disease is essentially one of middle life; nearly 70 per cent. of our cases occurred between thirty-five and sixty years of age. The age incidence grouped in decades is shown separately for males and females in Table II.

TABLE II.

	21-30.	31-40.	41-50.	51-60.	61-70.
Males . . . . .	4	12	16	7	6
Females . . . . .	7	5	11	7	0

There does not appear to be a very marked difference between the age incidence of the disease in males and females, except that in the latter it is possibly rather commoner below thirty years of age, whereas in males the disease occurs rather more commonly late in life.

It has been suggested by Hunter<sup>31</sup> that Addison's anæmia has a definite seasonal incidence. With a disease whose onset is so insidious it is naturally difficult to determine exactly in what month the onset occurred in any particular case. Judging by the dates at which patients were admitted to hospital either for the first time or with relapses, there does not appear to be any evidence of seasonal incidence. Out of ninety-four admissions forty-three occurred during the six winter months and fifty-one during the six summer months.

*Colour of Skin*

Of the seventy-five cases no less than sixty were noted as lemon-yellow or yellow in colour. Two cases were said to be "greenish." In three cases there was no note in the report as to colour, and ten cases were said to be "pale" or "sallow" in complexion. One case (No. 84) which showed no lemon-yellow colour in the ward subsequently developed it when seen by one of us after leaving the hospital. During remissions the yellow colour often completely disappears, only to reappear on the patient relapsing. Four cases were definitely jaundiced (Nos. 9, 53, 83 and 90), but in all of these cases there was definite evidence, either clinical or post-mortem, of cholecystitis.

The typical lemon-yellow colour would appear to be one of the most important and characteristic symptoms of the disease, and it is probable that were every case to be watched throughout its course it would be found to be invariably present.

*Gastro-Intestinal Symptoms*

In any attempt to estimate the frequency of the occurrence of gastro-intestinal symptoms in Addison's anæmia, we are faced with the difficulty of deciding to what extent any such symptoms as may be present are due to the administration of arsenic. In many cases patients had been treated with the latter before their admission to hospital, and unless gastro-intestinal symptoms were the first to appear it is almost impossible to exclude arsenic. On the other hand, a large number of the cases suffered from diarrhœa and vomiting, which could be definitely attributed to arsenic, and which ceased on stopping its administration. In going through the present series of cases we have endeavoured only to take account of gastro-intestinal symptoms where arsenic did not appear to be a factor.

Of the seventy-five cases in the series, forty-nine, or 65 per cent., suffered from gastro-intestinal symptoms of one kind or another, which appeared to be in no way connected with arsenic. In twenty-six cases (35 per cent.) the gastro-intestinal symptoms occurred either as the first symptom or very early in the development of the disease. Diarrhœa was noted in nineteen cases (25 per cent.). Vomiting occurred in thirty-six cases (47 per cent.). In twelve cases (16 per cent.) there was a long history of dyspepsia or indigestion, which had been present for many years before the onset of the anæmia. In twenty cases out of the seventy-five it was definitely stated that gastro-intestinal symptoms were not present, and in five cases no information was given on the subject.



These results agree very closely with those found by earlier workers. Hale-White came to the conclusion that vomiting and diarrhœa occurred in about half the cases, and French found that 66 per cent. had gastro-intestinal symptoms of some sort—almost exactly the figure found in the present series.

*Gastric analysis.*—Of the seventy-five cases in the present series an examination of the gastric contents was made in twenty-five cases. The more recent cases had a fractional test-meal performed, while the earlier cases in the series had the Ewald test-meal. Twenty-four cases showed complete absence of free hydrochloric acid. One case (No. 93) had no test-meal when in hospital originally, but when seen by us seven years later had a normal acid curve. Her hæmoglobin at this time was 84 per cent., and she had been free from any symptoms for over seven years.

In the cases in which fractional test-meals were performed the emptying time as judged by absence of starch and sugar was unduly rapid in three cases, normal in four cases, and showed delay in one case.

Four cases were examined during remissions of symptoms. In No. 83 the hæmoglobin was 82 per cent., in No. 85 it was 70 per cent., in No. 86 it was 80 per cent., and in No. 91, when she had been four years without any symptoms, it was 82 per cent., at the time when the test-meal was examined. In each case the gastric contents showed complete achlorhydria. With the exception of one patient (No. 93), whose gastric contents were examined seven years after her discharge from hospital, all the cases in the series showed complete absence of free acid. The bearing of this fact on the pathology of the disease is discussed later.

Unfortunately in the earlier series collected by French only three patients had their gastric contents examined. One of these, who appears to have been a typical case of the disease and exhibited typical post-mortem appearances, is noted as having an "abundance of free hydrochloric acid" in the gastric juice. The other two patients both had deficient or absent acid.

In 107 cases of Addison's anæmia quoted by Levine and Ladd where test-meals were performed, only in one undoubted case of the disease was free acid present.

*The tongue.*—In nineteen cases out of the seventy-five in the series there are notes as to the condition of the tongue and mucous membrane of the mouth.

In five cases the tongue was definitely stated to be normal and there was no history of sore tongue or mouth; in one case there was leukoplakia; in eight cases the tongue was said to

have been sore; in three cases there was ulceration of the mucous membrane of the mouth; and in one case the tongue was said to be "fissured."

From the above particulars it would appear that in only fourteen cases out of seventy-five was there any condition in the mouth severe enough to be noted in the reports. Naturally it does not follow from this that none of the other sixty-one patients suffered from glossitis, but were the condition as invariable as Hunter maintains, it is a remarkable fact that it should have been overlooked so frequently.

#### *Neurological Symptoms*

In the consideration of neurological symptoms and signs, just as in the case of the gastro-intestinal symptoms, there is often a difficulty in deciding whether arsenic is responsible, or whether the cases are true examples of degeneration in the spinal cord. Here again we have attempted to exclude all cases in which arsenic might have played a part.

In fourteen cases out of the seventy-five definite signs and symptoms of cord lesions appeared to be present. Of the fourteen cases eight showed signs of a combined lesion both of lateral and posterior columns, four were of a spastic type with exaggerated knee jerks and extensor plantar reflexes, and two were of a tabetic type. In only one (No. 13) could any record of a histological examination of the cord be traced, and these sections showed typical degeneration in both lateral and posterior columns.

The percentage of cases with neurological signs is 18. This figure is low compared with that found by French, who states that 65 per cent. showed signs or symptoms of nervous disorder. On examining his case reports, it would appear that he included many cases, whose symptoms were purely subjective, such as buzzing noises in the ears, giddiness and headaches, which may well have been due to the anæmia, rather than any organic nervous lesion. In his series French appears to have had only six cases with definite signs of subacute combined degeneration (9 per cent.); but there were five others with very suggestive symptoms. In the series quoted by Cabot 10 per cent. showed signs of degeneration of the cord, either of the spastic or tabetic type.

In a recent series from the Mayo Clinic, Woltmann<sup>24</sup> stated that after a careful routine examination of the nervous system, it was found to be affected in 80 per cent. But only 26 per cent. had an extensor plantar reflex, and knee jerks and ankle jerks were absent in 7 and 21 per cent. respectively. Romberg's

sign was present in over 50 per cent., but in a patient with severe anæmia this cannot be taken as diagnostic of nervous disease.

It has long been recognised that the neurological signs and symptoms of subacute combined degeneration may antecede the anæmia, and in one case (No. 85) the patient first came under observation for difficulty in walking and ataxia. Though the blood film has shown changes very typical of Addison's anæmia, the degree of anæmia has never been very severe. Another case, not included in the series, has recently come under our observation with typical signs of subacute combined degeneration, but with no appreciable anæmia, and no blood changes suggestive of Addison's anæmia. In the latter case it is interesting to note that the gastric contents show complete achlorhydria.

#### *Pigmentation in Addison's Anæmia*

The occurrence of pigmentation both in the skin and in the buccal mucosa has been described by Hale-White and later by French. Among the sixty-eight cases analysed by the latter, pigmentation of the skin was present in twelve and pigmentation in the mouth in two cases. Here again we are faced with the old difficulty of deciding how far arsenic is responsible. In the present series of cases sixteen, or 21 per cent., showed pigmentation. Of these, seven presented some symptoms of arsenical poisoning, and quite possibly their pigmentation may have been due to this cause. In the remaining nine, if arsenic was responsible, there was no evidence of other arsenical symptoms, such as gastro-intestinal disturbances or peripheral neuritis.

In four cases there were patches of brown or black pigment in the mucous membrane of mouth or lips. One of these is remarkable as having been diagnosed as Addison's disease (see Appendix B, No. 35). A very similar case has come under the notice of the writers, but for lack of definite evidence as to the diagnosis he has been included among the doubtful cases (Appendix A, No. 89). The patient is a man aged forty-two, with a history of muscular weakness and vomiting over a period of two years. When first seen his blood pressure was 120 mm., but later dropped as low as 80 mm. On admission he was pigmented all over, but particularly in the axillæ, groins and perineum. There were a few small spots of brown pigment on the gums where his dentures exerted pressure. The skin round the anus was pigmented. When first seen he was regarded as suffering from Addison's disease, but while in hospital he developed a severe anæmia of the Addisonian type with hæmoglobin down to 27 per cent. After blood transfusion he improved, and when

last seen was not markedly anæmic. The spleen was easily palpable, the liver enlarged, and his gastric contents have shown achlorhydria on three occasions. While in hospital a suprarenal graft from a fœtus was inserted into his testicle.<sup>27</sup>

These two cases illustrate how difficult the differential diagnosis between Addison's disease and Addison's anæmia may be. It would appear quite definitely that the presence of buccal pigmentation occurs in a small percentage of cases of Addison's anæmia, while pigmentation of the skin is relatively common. A low blood pressure is of no value in the diagnosis between the two conditions, as it may be very low in Addison's anæmia. Of seven cases examined by one of us (J. J. C.), the systolic pressures were below 100 mm. of mercury in five, and above that figure in two. The lowest pressure was 70 mm. and the highest 135 mm. In Addison's anæmia, as indeed in any severe anæmia, the blood pressure falls to a point quite as low as in many cases of Addison's disease. During remissions of the anæmia, when the patient is up and about, it may rise again to approximately normal.

It has been suggested recently <sup>4</sup> that white hair is an almost constant feature of Addison's anæmia. At first we were rather impressed by this, but later saw several typical cases without it, and on reviewing the cases as a whole and remembering the age incidence, we do not think there is any evidence that it is specially common.

#### *Duration of Symptoms*

Of the seventy-five cases in the series, forty-three either died in the hospital or were ascertained to have died subsequently. The duration of symptoms from the commencement of the disease to death (or to March 1922) is shown in Table III.

TABLE III.

	Of 43 cases who died.	Of cases still alive.
Under 1 year . . . .	5	1
1 to 2 years . . . .	15	3
2 to 3 years . . . .	12	3
3 to 4 years . . . .	5	1
4 to 5 years . . . .	1	1
5 to 6 years . . . .	2	1
Above 6 years . . . .	3	3

In one patient, who is still alive (No. 83), symptoms have been present for over nine years, and during the course of the disease there have been several remissions during which the patient has been able to return to work. The case is in every way typical of Addison's anæmia, except that there is clinical evidence of cholecystitis and nephritis in addition to the anæmia.

No attempt has been made to analyse the number and duration of remissions, as the subject has already been fully dealt with by Hunter and by Cabot. Except for a comparatively small proportion of acute cases, most of the patients showed evidence of either partial or complete remissions of their anæmia.

#### *Changes in the Blood*

The condition of the blood in Addison's anæmia has been studied very fully, but there are some points to which it is worth while drawing attention. The undoubted fact that some cases, which are ultimately proved to be Addison's anæmia, have on one or more occasions shown blood changes not characteristic of that condition, has led some observers to minimise their importance. No. 87 on admission had a hæmoglobin percentage of 20 with a colour-index of 0.6, slight anisocytosis and only a few nucleated red cells. The white count was 9000. From this blood examination alone it would have been difficult to reach any conclusion, though a history of vomiting, a palpable spleen and an extensor plantar reflex made the diagnosis certain. Five months later he was seen during a period of hæmolysis. He was lemon-yellow with a hæmoglobin percentage of 27 (it had certainly risen to 60 and perhaps higher in the interval) and a colour-index of 1.3. There was marked aniso- and poikilo-cytosis, with punctate basophilia. Megaloblasts were present and the white cells had fallen to 5000.

No. 88 had a typical blood film, but a colour-index of 0.5, with 10,000 white cells. Two months later repeated counts gave a colour-index of over 1.1 and a white count of 3000.

It is certainly true that a single blood count may be misleading, but in all cases observed over any length of time a study of the blood alone, or of the clinical findings alone, would be sufficient to lead to the correct diagnosis.

*The Colour-index.*—The value of the raised colour-index in diagnosis has been especially called in question. If a colour-index of above or below unity is the only criterion, a low colour-index is certainly not against a diagnosis of Addison's anæmia, for in French's series of nearly 400 blood counts the colour-

index was above one only in 60 per cent., and in this series in 71 per cent. of the cases.

But owing to the figure arbitrarily chosen for the hæmoglobin standard, many healthy persons have a colour-index of 0·9 or 0·8, and if this be accepted a subnormal colour-index is rare in Addison's anæmia.

The following table shows the colour-index found in 200 more or less complete blood counts in this series, and in the first hundred blood counts given in French's series.

TABLE IV.

Colour-index.	0·5-0·6.	0·7-0·9.	1·0-1·2.	1·3-1·5.	1·6 and above.
Percentage of cases of :—					
(a) this series . . .	5	24	39	23	9
(b) French's series . .	7	29	39	12	13

The agreement is sufficiently close to show that the figures are accurate. In only one case in this series was there a reliable blood count with a colour-index of 0·5.

A further point is observed in the diagram (Fig. 1). The colour-index is plotted against the hæmoglobin percentage in cases of Addison's anæmia (marked with a dot), and in cases of chlorosis and secondary anæmias from the reports of the same period (marked with a cross). These are indicated by the same sign, because the original chart did not show that the colour-index was any lower in chlorosis than in other secondary anæmias.

The striking point is that in secondary anæmia the colour-index tends to fall with the hæmoglobin percentage, while in Addison's anæmia it tends to become more variable. There is very little overlapping of the two groups. A colour-index of under 0·7 over a long period is never found in Addison's anæmia, but a colour-index between this figure and unity is almost as common as one between unity and 1·2, and quite as common as one between 1·3 and 1·6.

*Changes in size and shape of the red cells.*—The other point in the blood examination which seems to be of special importance because of its constancy is the presence of marked aniso- and poikilo-cytosis.

Of the seventy-two cases in which a blood film was available, only two were stated to have slight aniso- without poikilo-cytosis, and only six to have moderate poikilo-cytosis without any reference to aniso-cytosis. In practically every case

marked aniso- and poikilo-cytosis was present at some stage of the disease.

The size of the red cells is so variable that it is not easy to form a correct estimate of the average size of the corpuscles, but very careful counts by Price Jones<sup>7</sup> have shown that the average size of the corpuscles is increased from  $7.2\mu$  to  $8.2\mu$ .

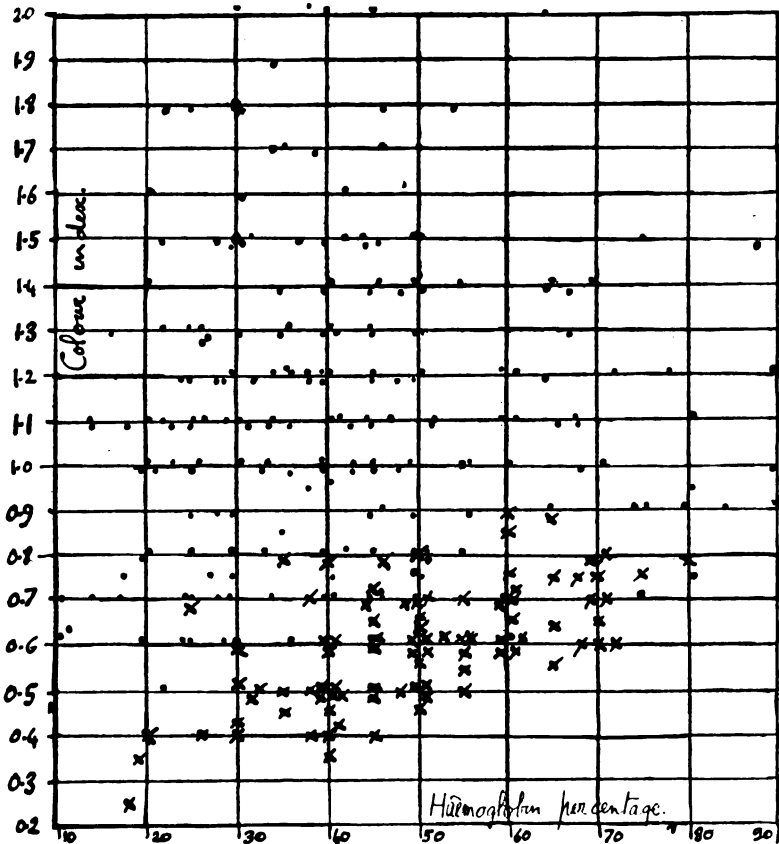


FIG. 1.

Showing the relationship between hæmoglobin percentage and colour-index.

. blood counts in cases of Addison's anæmia.

× blood counts in cases of chlorosis and secondary anæmias.

Capps,<sup>8</sup> using a less accurate method, found many years ago that the average size was increased from  $7.6\mu$  to  $8.0\mu$ .

Another method of investigating the size of the red cells is available, if simultaneous determinations are made of the hæmoglobin percentage, red cell count and the ratio of the volume of red cells to the volume of the whole blood. This method has recently been fully described by one of us (J. M. H. C.),<sup>9</sup> but a summary is added here.

Venous blood is withdrawn with a syringe, and is at once mixed with crystals of potassium oxalate, sufficient to give an 0.5 per cent. solution of potassium oxalate. This prevents clotting and does not interfere with the subsequent determinations. This method has been used for most of the blood counts we have done, as well as for the hæmatocrit determinations. It has been found very convenient, especially as the whole blood count need not be finished immediately, and there is always enough blood for duplicate determinations. With blood obtained by pricking the finger, it was impossible to get a constant percentage of potassium oxalate, so this method was not used for any hæmatocrit determinations.

The hæmoglobin percentage was found with a specially standardised Haldane-Gowers hæmoglobinometer.

The red blood corpuscles were counted with a Bürker-Zeiss hæmocytometer, and at least two thousand were counted in each case. To find the relative volume of the red cells and whole blood the following method was used. Glass tubing was drawn out to capillary bore. Any part with obvious change of diameter was thrown away and the remainder cut up into capillary tubes of the required length. The blood was well mixed and six tubes were dipped in it, until the blood had risen almost to the top. The top was then sealed off in a flame, care being taken that the blood itself was not burnt. The six tubes were then rotated for fifteen minutes in a centrifuge, as this time was found sufficient to give constant results. Six tubes were always used and an average taken, so that any error of technique might be minimised. The lengths of the columns of corpuscles and of whole blood were then measured. In normal blood the corpuscles were found to occupy 40 per cent. of the total. In the blood of various anæmias the relative volume occupied by the corpuscles was expressed as a percentage of the normal figure (40 per cent.), so that comparisons could be made directly between the hæmoglobin percentage, the red cell count percentage and the red cell volume percentage. From these three figures the "colour-index" and "volume-index" were obtained by dividing the hæmoglobin and the red cell volume by the red cell count, all being expressed as percentages. The volume-index gives a guide to the relative size of the average red cell, and as it was found that over very wide variations of hæmoglobin percentage and colour-index there was only a slight difference between the volume-index and the colour-index, it follows that the colour-index is a rough guide to the size of the average red cell. If the ratio of colour-index to volume-index was quite constant, it would mean that the proportion of hæmoglobin in every



corpusele was the same and that the amount of hæmoglobin in the corpusele depended only on its size. This was almost but not quite true.

Complete results were obtained in eight cases of Addison's anæmia. The average red cell percentage was 29 and varied between 12 and 50. The average hæmoglobin percentage was 34 and varied between 16 and 65. The average percentage volume of the red cells was 16, *i. e.* 41 per cent. of the normal figure. The average colour-index and volume-index were 1.24 and 1.39.

In these eight cases, where the hæmoglobin was reduced nearly 70 per cent., the size of the average red cell was increased nearly 40 per cent., in spite of the presence of numerous microcytes. From this the increase in diameter can be calculated, and is found to agree fairly closely with the direct measurements already quoted.

A hæmatocrit determination may sometimes be of help in diagnosis, because, although the changes in volume-index and colour-index are generally parallel, in any particular case the volume-index may be increased more than the colour-index.

One can conclude that there is little or no change in the concentration of hæmoglobin in the corpusele in Addison's anæmia. The increased colour-index is amply explained by the increased average size of the red corpusele, and this increased average size is of even greater importance than the aniso-cytosis.

*Other changes in the red cells.*—Other changes in the blood film are less constantly present. For example, in the sixty-eight cases in which information was available nucleated red cells were present in fifty-eight and absent in ten, while megaloblasts were only present in twenty-nine and were absent in twenty-one. Perhaps if the cases had been examined sufficiently frequently normoblasts and megaloblasts would have been found in all at some time in the course of the disease.

But from the practical point of view, though the presence of megaloblasts in an adult with anæmia is a strong argument in favour of the anæmia being Addisonian, the absence of megaloblasts and even of nucleated red cells is no argument to the contrary.

The same may be said of polychromasia and punctate basophilia. One or both were present in thirty-nine cases, but both were absent in six cases, where a careful examination was made.

*Changes in the white cells.*—Taking 5000–7000 per c.mm. as the normal limits of the white cell count, fourteen cases were normal. Eight cases had an increased white count, but this

was never above 10,000, and forty-six cases had a definite leucopenia—twenty of these being under 3000.

A relative lymphocytosis was a striking feature of some cases, and the meaning of this is made clearer if the number of polymorphonuclear cells and lymphocytes per c.mm. is calculated. Taking 1200–2400 per c.mm. as the normal limits of variation for the lymphocytes, thirty-two cases fell within normal limits; in fifteen the white cells were reduced, and in four only were they increased. Taking 3000–5000 per c.mm. as the normal limits for the polymorphonuclear cells, only three showed an increase, while thirty showed a diminution, and often a very considerable diminution, and eighteen were within normal limits, though ten of these were very near the lower limit.

Seven cases showed a percentage of eosinophil cells above 5 per cent. In one of these it was constantly present and varied between 9 and 20 per cent. But most of these seven had leucopenia and only three showed an actual increase of eosinophil cells, and in none of these three was it more than twice the normal figure.

More shortly, 70 per cent of cases showed leucopenia, 20 per cent. a normal, and 10 per cent. a slightly increased white count. In nearly 65 per cent. the number of lymphocytes was normal, and in 30 per cent. it was somewhat reduced. In 60 per cent. the number of polymorphonuclear cells was reduced—sometimes very considerably—and in a further 20 per cent. it was near the lower limits of the normal range of variation.

*Changes in fragility of the red corpuscles.*—McNeal,<sup>11</sup> using solutions of NaCl of various strengths, found that the fragility of the red cells in Addison's anæmia was slightly increased, but very nearly normal. Giffen and Sanford<sup>22</sup> found the fragility slightly diminished.

Using the same method in some cases of this series, Ryffel found the fragility slightly increased in No. 29 and normal in No. 83, and we found it normal in Nos. 85, 93 and 95 and slightly diminished in Nos. 86 and 90.

One can conclude that with this method there is little if any change in Addison's anæmia. Using saponin to produce hæmolysis, Bigland<sup>10</sup> found there was a slight increase, and McNeal<sup>11</sup> found a rather greater increase in the fragility.

The test is only of importance in helping to exclude cases of acholuric jaundice, which might sometimes be confused with Addison's anæmia. There was one such patient in this series, who had been in hospital in 1895 and again in 1909, before this test had been introduced. He is still alive and is a well-marked case of acholuric jaundice.

*The clotting time.*—Using the method of Dale and Laidlaw,<sup>23</sup> Ryffel<sup>26</sup> found that the clotting time was increased, *e. g.* No. 36, 2' 24'', No. 43, 2' 19'' and No. 83, 2' 18'', the normal figures varying between 1' 40'' and 1' 50''.

In Nos. 129 and 128, which are not included as definite cases of Addison's anæmia, it was slightly increased, to 2' 0'' and 2' 5'' respectively. We found it definitely increased in three—in No. 83, 2' 25'', in No. 86, 2' 10'', and in No. 90, 2' 20''.

*Wassermann reaction.*—This was only done in a few cases, except those which have recently been in hospital. It was negative in ten. It was positive in No. 26, which was a typical case with no clinical evidence of syphilis, and in No. 104, which had clinical evidence of syphilis and was not included as a case of Addison's anæmia.

No. 110 had a strongly positive Wassermann with no clinical evidence of syphilis, but six months later, without very thorough anti-syphilitic treatment, she had a negative Wassermann. She has not been included as a definite case of Addison's anæmia because her blood count and the course of the disease were not characteristic.

Like others, we have not found any evidence that syphilis is a factor in the etiology of Addison's anæmia.

### *Pathology*

There are three ways in which a severe and chronic anæmia may arise, and at different times Addison's anæmia has been attributed to all these causes.

(a) *Loss of blood by hæmorrhage.*—This was excluded in Addison's original description. Three cases, which were diagnosed as Addison's anæmia, proved to be anæmic from long-continued loss of blood from hæmorrhoids, and it is interesting to compare their blood picture and clinical condition with the true cases.

No. 111 had hæmorrhoids for seventeen years and finally developed a severe anæmia. The diagnosis of Addison's anæmia should have been made with great reserve, because his white count was 11,000 and he never showed a lemon-yellow colour. His symptoms and anæmia were cured by operation, and three years later he was perfectly well. His hæmoglobin went down to 35 per cent., and he had aniso- and poikilocytosis and nucleated red cells in his blood film.

No. 112 was alive and fairly well fifteen years after her first admission to hospital. She had been seen at intervals all the time and had always been anæmic, but only on one occasion was a diagnosis of Addison's anæmia made. Her colour-index

was generally low, and once only 0·4. Two nucleated red cells only were seen on one occasion, and the only time that anisocytosis was found the majority of the cells were of small size.

No. 116 never had a yellow colour and had only very slight changes in his red cells. He was in perfect health eight years after he had been in hospital, and said that he had then lost much more blood from hæmorrhoids than at any other time. A test-meal while his hæmoglobin was 40 per cent. showed hypochlorhydria, but the gastric contents were acid to dimethyl.

In the other two there was unfortunately no record of a test-meal.

Hæmorrhoids had been present for long periods in three others (26, 59 and 61), but they appeared typical cases of Addison's anæmia, and in one an operation for hæmorrhoids did not produce any general improvement.

The tendency to hæmorrhages terminally has long been recognised and was found in nineteen cases in this series. In four of these the hæmorrhage seemed to be an earlier and more important factor. No. 2 (see Appendix) started with severe bleeding from the gums, and had severe uterine hæmorrhage during her illness, but post-mortem there were typical appearances of Addison's anæmia. No. 32 started with severe bleeding from the nose, which recurred frequently through his illness, but the typical blood count and the remissions until his death in the influenza epidemic five years later seemed to confirm the diagnosis. Nos. 37 and 92 had similar symptoms throughout their illness.

No. 113 (see Appendix) suggested a possible association of nephritis and hæmaturia with Addison's anæmia. He had a yellow colour, several remissions, typical blood changes, and a Prussian blue reaction in the kidneys after death. But the other post-mortem changes and the normal test-meal during life have prevented his inclusion as definite Addison's anæmia.

In Nos. 68, 83 and 88, who had chronic nephritis (in one with severe and continued hæmaturia), this condition seemed to be secondary to the anæmia and not the cause.

Gulland<sup>34</sup> described some anomalous cases of Addison's anæmia, three of which were associated with chronic renal disease. In two of these there was a considerable leucocytosis, which makes the real diagnosis very doubtful in the absence of post-mortem confirmation. No. 113 had leucopenia throughout.

While writing this paper three cases of chronic nephritis with severe anæmia were seen, but in none of these were the

blood pictures or the other clinical findings in any way characteristic of Addison's anæmia, except that in two of them the colour-index was higher than in other secondary anæmias.

There is no evidence that loss of blood, even over long periods, can produce the blood picture or clinical features of Addison's anæmia.

(b) *Deficient blood formation.*—A failure in the output of red cells has been excluded as the cause of Addison's anæmia by Pepper's discovery that the bone marrow was red and contained active regenerating tissue.<sup>12</sup> But the theory has been revived in another form—that the bone marrow produces abnormal red cells, which are easily destroyed in the body. This would account for the increased destruction of red cells, which is the most essential point yet discovered in the pathology of Addison's anæmia. The strongest argument against this view, and in favour of the third possibility, is the close resemblance between Addison's anæmia and the anæmias produced by infection with *Bothriocephalus latus*, and experimentally by poisoning. These are discussed in more detail later.

Aplastic anæmia, where the bone marrow is normal, other things being characteristic of Addison's anæmia, is also against the importance of the bone marrow as the primary factor. Nos. 7, 28 and perhaps 101 were examples of this.

(c) *Increased blood destruction.*—The arguments in favour of this are clear and conclusive. The increased deposit of iron in the liver, spleen and kidneys is the most important.<sup>28</sup> This occurs sometimes in other diseases, *e. g.* in some cases of lymphatic leukæmia and Hodgkin's disease, and in general infections where there is a rapid destruction of red cells. But it is constantly present in Addison's anæmia.

In this series there were twenty-two cases in which an autopsy was performed, and the Prussian blue reaction was found to be positive in the liver in twenty-one, in the spleen in fourteen, and in the kidneys in sixteen. In the others, not included as Addison's anæmia, it was present in the liver in four cases—two of leukanæmia (114 and 118), one of myx-œdema with anæmia (115), and one of septicæmia (117). In the latter the reaction was also positive in the spleen and kidneys, and in 113 it was present in the kidneys only. These cases are fully described in the Appendix.

Other arguments in favour of this increased destruction are the constancy of the yellow colour due to changed blood pigment deposited especially in the fat, the increased pigment in the serum, and the excess of urobilin in the urine.

The experimental work shows that Addison's anæmia is

due to increased blood destruction from some chemical or bacterial toxin. Numerous workers have produced a severe anæmia with the typical blood picture with quite different poisons. Hunter <sup>16</sup> made use of toluene diamine, Paton and Goodall <sup>13</sup> and Price Jones <sup>14</sup> of phenyl hydrazine, and Bunting <sup>15</sup> of ricin and saponin.

In all these experiments the blood showed a marked reduction in the number of red cells, a high colour-index, large red cells of unequal size and shape with many nucleated forms and basophil staining. The iron reaction was given by the liver, spleen and kidneys, its intensity depending on the rate of production of the anæmia. In several cases where the poison was given in large doses there was actually hæmoglobinuria. A megaloblastic reaction was found in the bone marrow. There was an absence of leucocytosis, though leucopenia was not often observed. Sometimes the spleen was enlarged. There is no mention of neurological or gastro-intestinal symptoms, but the presence of these might well depend on the poison acting over a longer period.

In the rabbit the anæmia following frequent hæmorrhages always shows some of the features of Addison's anæmia—certainly more so than in a similar anæmia in man. But Price Jones <sup>17</sup> made a careful comparison of the anæmias following hæmorrhage and poisoning with phenyl hydrazine, and found that the latter was much more like Addison's anæmia.

It has long been known that the anæmia following infection with *Bothriocephalus latus* closely resembles Addison's anæmia. Schauman and Tallquist <sup>18</sup> showed that this anæmia could be produced in dogs by injection of filtered extracts of this tapeworm or by giving these by mouth. In some animals examined after death the liver and spleen gave a Prussian blue reaction, and the bone marrow was red.

Finally, McLeod and McNee <sup>19</sup> showed that a like blood picture could be produced by the injection of a hæmolysin obtained from virulent streptococci. In one rabbit, which died rapidly after an anæmia produced by a hæmolytic serum,<sup>21</sup> a gelatinous condition of the marrow was found very similar to that found in aplastic anæmia, while in all the others a megaloblastic bone marrow was found. The Prussian blue reaction for iron was also found in the liver, kidney and spleen.

If it is agreed that the cause of the disease is an increased blood destruction due to some poison, there remain two questions of special interest. Is the poison a chemical substance analogous to those used in most of the experimental anæmias, or is it some

bacterial product as in the above-quoted experiment? And from what part of the body may the poison come?

Because the iron reaction is found most constantly in the liver, Hunter thought that the poison must come from the portal area and presumably from the gastro-intestinal tract. Recently McMaster, Rous and Larimore<sup>20</sup> have shown that this assumption is not valid. If the hæmolysis takes place quickly, the pigment circulates in the blood and is excreted by the kidneys, where some of it is retained and gives the Prussian blue reaction. If the destruction takes place less quickly, this test will be given by the liver and not by the kidneys.

Another argument in favour of a gastro-intestinal origin is the frequency of early symptoms affecting the gastro-intestinal tract—symptoms which do not occur in other anæmias. In this series, after carefully excluding diarrhœa and vomiting, which might be due to arsenic, one or both of these were present in 65 per cent. In 35 per cent. they occurred as the earliest, or almost the earliest, symptoms.

Even if diarrhœa was present in every case, it does not follow that the intestine is the source of the infection. Ryle<sup>35</sup> refers to the constancy of diarrhœa in streptococcal septicæmia, whatever the primary focus of the septicæmia. Similarly the diarrhœa might be secondary to the general disease, or might follow the achlorhydria.

In practically 100 per cent. of cases of Addison's anæmia examination of the gastric contents shows complete absence of free hydrochloric acid, and sometimes this has been proved to precede the development of the anæmia.

In seven cases there was some evidence that uterine sepsis or hæmorrhage preceded the onset of the anæmia. Three of these, Nos. 2, 42 and 93, are described in the Appendix. In No. 2 there was the unusual symptom of constipation, in No. 42 slight diarrhœa, in No. 93 no vomiting or diarrhœa, and in Nos. 43, 104 and 105 only slight vomiting, so that gastro-intestinal symptoms seemed equally common in this group. It is unfortunate that a test-meal was not done in any of these cases while they were anæmic, because if achlorhydria is also present in them, it would show that the uterus is not the primary focus of infection, or that the achlorhydria is not a causal factor in allowing the passage of organisms from the mouth. This point cannot yet be decided. Cabot believes that these cases really belong to a different group, but it is difficult to see any justification for this in the other chemical or hæmatological findings.

In No. 94 (see Appendix), where the disease followed chronic

suppuration of the frontal sinus, diarrhœa and vomiting were early symptoms. The association may have been a coincidence, or the gastro-intestinal tract may have been infected from the sinus, as in other cases it seems to be from the teeth.

In No. 95 chronic bronchitis sufficiently severe to have needed twelve admissions to an infirmary may have been a source of infection. Vomiting was one of the early symptoms and a test-meal showed achlorhydria.

Phthisis and the associated lung infection may have been the primary source in one case (35 in Appendix). Diarrhœa was present, but no test-meal was done.

In No. 113, where the anæmia may have been associated with suppuration in the kidney, and in No. 115, where it was associated with very severe pyorrhœa and oral sepsis, there were no gastro-intestinal symptoms, and in both test-meals were normal. It is interesting that quite apart from the presence of free acid in the gastric juice, neither of these were included as proved cases of Addison's anæmia on clinical and hæmatological grounds.

No. 117 is of special interest, because he had some very acute infection, which rapidly caused death with post-mortem changes characteristic of Addison's anæmia. There were no gastro-intestinal symptoms and no test-meal was done. He is not included as a certain case, but probably the same process was at work here more acutely.

There is no definite proof of the source of the blood destruction, but there is some evidence that while the gastro-intestinal tract is the most common cause, infection in other parts of the body may also give rise to typical Addison's anæmia.

Little has been said about oral sepsis in the production of Addison's anæmia. Dental caries and pyorrhœa alveolaris are so common in hospital patients of this age, that the mere presence of these is of little importance. It is certainly true that the removal of oral sepsis will frequently improve patients with Addison's anæmia. It is equally true that severe anæmias which are not of an Addisonian type may be cured by the removal of oral sepsis. Hunter is probably right in suggesting that in many cases two factors are at work, one producing a true Addison's anæmia and another a septic anæmia; and that the cure of the latter is one of the factors which have improved the prognosis in Addison's anæmia.

No. 93 (see Appendix) is of interest because with her recovery took place without any local treatment for her oral sepsis.

Whatever part of the body may provide the primary source, it is still uncertain whether there may be poisoning with some



simple chemical substance introduced directly or produced by abnormal bacterial changes in the intestine, or an infection with hæmolytic streptococci, bacteria, or perhaps protozoal organisms. The similarity with *Bothriocephalus* anæmia might even suggest a metazoal infection, but it is unlikely that this would have escaped detection.

There are several arguments which have been used in favour of an infection.

The frequent presence of pyrexia is one. In these cases thirty-six, or 50 per cent., showed definite pyrexia at some period while they were under observation, and a further 25 per cent. had slight pyrexia. Certainly high pyrexia was not common, but it was observed in some cases.

The enlargement of the spleen has been used as another argument. In the twenty patients who died in hospital the spleen was below 150 grms. in five, the lowest weight being 90, and normal in two cases. It was above 150 in thirteen cases, reaching the weight of 1400 grms. in one case, but only 500 grms. in the next largest.

In the eleven patients who are still alive and have been seen by the writers the spleen was palpable. Certainly the spleen is enlarged in the majority of cases before death, though if the series be taken as a whole, and it is assumed that the spleen was not enlarged where no notes were made in the report, there was only clinical evidence of enlargement in 30 per cent. of the cases, a very similar proportion to that found by French.

It is possible that the splenic enlargement and the lesser degrees of pyrexia might be associated with blood destruction rather than infection. Where there was considerable pyrexia it is more difficult to suppose this, but in such cases the high temperature was usually due to a terminal secondary infection.

Hurst has laid stress on the fact that *streptococcus longus* has been found with great frequency in the duodenum as well as in the mouth and fæces, but their presence in the mouth and fæces is too frequent in other subjects for this to be at all conclusive until further tests of their specificity have been found.

Recently Hurst<sup>33</sup> has laid great stress on the importance of achlorhydria as a causal factor in Addison's anæmia. He thus summarises the pathology of the disease in a single sentence: "The achlorhydria allows the bacteria which produce the hæmolytic toxins, and which probably have their primary focus in the mouth, to pass through the intestine without being destroyed by the hydrochloric acid, which ought to be present." In a recent verbal communication Hurst has amplified this view by suggesting that the bacteria act upon the proteins which have

been insufficiently digested owing to the absence of gastric juice and the associated pancreatic achylia, with the result that hæmolytic toxins are produced.

There are certain difficulties in accepting the view that the disease is simply a chronic streptococcal infection of the upper alimentary tract. Firstly, signs of inflammatory reaction in the intestines are not a constant post-mortem finding. Secondly, the white blood count is totally unlike that usually found in streptococcal infections. Lastly, were streptococci the infective agent it might be expected that they would be agglutinated by the patient's serum, or that, if a vaccine was prepared from them, its injection would produce a reaction. Nor is it easy to believe that the organisms produce a hæmolytic bacterial toxin within the lumen of the intestine, which could be absorbed through an intact mucous membrane.

What then is the significance of the achlorhydria in Addison's anæmia? All the patients in this series in whom test-meals were performed during the active stage of the disease showed complete achlorhydria. Three cases examined during remissions also gave a similar result, in spite of the fact that their blood was practically normal at the time. Such results confirm the observations of others, and suggest that achlorhydria is not so much due to the anæmia as a causal factor in the production of the disease. Quite apart from the fact that in a few cases achlorhydria has been shown to be present even for years before the onset of the anæmia, there does not appear to be any evidence that a severe anæmia of long standing necessarily does more than cause some degree of hypochlorhydria. We have done test-meals in three cases of splenic anæmia and found complete achlorhydria of the type found in Addison's anæmia in two cases, while in the third free acid was present in one specimen in very small amounts. On the other hand, one case with a severe anæmia down to 17 per cent. hæmoglobin, which in some features resembled Addison's anæmia, showed on two separate occasions the presence of hydrochloric acid in small amounts in the fractional test-meal. Post-mortem the latter case was proved to be one of Hodgkin's disease.

In three other patients who have been under observation recently a severe anæmia has not been associated even with hypochlorhydria. A woman aged thirty-eight, with a three-years' history of splenomedullary leukaemia, was in hospital for four months, during which time her hæmoglobin varied between 30 and 50 per cent. Her fractional test-meal gave a curve just above the normal. A man of fifty-four with pyelo-nephritis, who was in hospital for two months, during which time his hæmo-

globin varied between 34 and 40 per cent., had definite hyperchlorhydria. A girl of twenty-one with severe chlorosis and hæmoglobin only 25 per cent., showed a normal curve with her fractional test-meal.

Herzog<sup>25</sup> describes a case of *Bothriocephalus* anæmia with a normal acidity, and states that achlorhydria is present in about half of these cases, but always present in Addison's anæmia.

If achlorhydria is an essential causal factor in the development of Addison's anæmia, what part does it play in the pathology of the disease? We have already stated some of the difficulties involved in the view that the lack of free acid in the stomach allows the passage of streptococci from the teeth to the intestines. Moreover, it must be remembered that in about one-third of all normal persons there is no free hydrochloric acid in the resting-juice.<sup>32</sup> Yet during the night, when the stomach is empty, saliva with organisms from the mouth and teeth are being constantly swallowed. The enlargement of the spleen and the pyrexia can be explained as the result of the hæmolysis, and the white blood count is absolutely unlike a coccal infection, though the *injection* of a streptococcal hæmolysin obtained *in vitro* did give rise to anæmia without leucocytosis.<sup>19</sup>

How then can the achlorhydria predispose to the development of Addison's anæmia? It is conceivable that under certain conditions brought about by achlorhydria chemical bodies might be formed from the breakdown of protein by bacteria not normally present; and that these could be absorbed through the stomach or intestines, and could produce hæmolysis. As an alternative theory it may be that the achlorhydria allows the invasion of some protozoal organism, possibly a spirochæte. The features of the disease such as the white count and the remissions are more suggestive of a protozoal than a coccal infection.

The close similarity to the anæmias produced by *Bothriocephalus* infections and experimentally seems a strong argument in favour of a similar cause in Addison's anæmia. The two arguments which are most difficult to reconcile with a streptococcal origin of the disease are the extraordinarily constant clinical picture of Addison's anæmia—a comparatively rare disease, while infections with hæmolytic streptococci are very frequent—and the definite remissions which are such a constant feature of the disease.

In no other condition are remissions such a marked feature, except in diseases which are proved to be or probably are due to a protozoal infection.

Everyone is agreed that the course of the disease has been

lengthened by vigorous treatment of septic foci, and that recoveries do take place, but it still remains true that in the majority of cases the disease runs its course with remissions and ends fatally. This should not be so, if the pathology were completely understood.

#### *Treatment.*

It is still true that treatment with arsenic is the most effective remedy at hand. There is no evidence from a study of these cases that injections of organic compounds of arsenic give more satisfactory results than arsenic by the mouth.

There is no doubt that many patients we have seen could not have been alive without blood transfusions, but its main rôle seems to be in tiding over the most dangerous time of the illness and raising the hæmoglobin sufficiently high for the bone marrow to take up again the task of producing new red cells. No. 83 is the best example of this.

The removal of focal sepsis seems the most rational line of treatment with our present knowledge, and the results in prolonging the course of the disease and improving the prognosis certainly seem to justify this treatment.

It is still too early to speak of the results of treatment with hydrochloric acid in large doses continued for long periods of time, so warmly advocated by Hurst.<sup>33</sup>

It seems that these three things—blood transfusion, vigorous treatment of focal sepsis and administration of hydrochloric acid—should certainly be added to the five things which Sir William Osler regarded as necessary in the treatment of Addison's anæmia<sup>36</sup>—a correct diagnosis, rest in bed, fresh air, good food and arsenic.

We are indebted to Dr. A. F. Hurst for his help and advice, and to Mr. E. R. Boland for assistance with blood examinations.

#### *Summary*

Addison's anæmia is a true clinical entity, with characteristic clinical features and a characteristic blood picture.

The following signs are constantly present:—

- (1) A severe anæmia with a colour-index over 0·6;
- (2) marked aniso- and poikilo-cytosis with the average size of the red cells increased;
- (3) absence of leucocytosis;
- (4) a lemon-yellow colour of the skin;
- (5) achlorhydria;
- (6) a Prussian blue reaction in the liver, spleen or kidneys;

- (7) red bone marrow in the long bones;
- (8) an increased clotting time.

In addition to the above, the following signs and symptoms are generally present :—

- (1) Nucleated red cells (in at least 85 per cent.), megaloblasts and basophil staining of the red cells;
- (2) a leucocyte count below 5000 (70 per cent.), with a relative lympho-cytosis, and absolute reduction in the number of polymorphonuclear cells;
- (3) a long course with a tendency to remissions (90 per cent.);
- (4) gastro-intestinal symptoms (65 per cent.);
- (5) Some enlargement of the spleen (65 per cent.);
- (6) some degree of pyrexia (50–70 per cent.);
- (7) a low blood pressure.

Other less constant, but very important features are :—

- (1) Signs and symptoms of degeneration in the lateral and posterior columns in the spinal cord (20 per cent.);
- (2) pigmentation of the skin and mucous membrane (20 per cent.);
- (3) glossitis (nearly 50 per cent. in cases seen recently);
- (4) a tendency to hæmorrhages.

In practically every case observed over a short period of time a diagnosis can be made from the clinical features or from the blood examination alone.

In the blood examination, a colour-index of under 0·7 is never found over a long period, but a colour-index between 0·7 and 1·0 is as common as one between 1·3 and 1·6.

In the blood film the presence of macrocytes and the absence of leucocytosis is the most constant and important feature, and normoblasts are present in the great majority of cases.

The changes in the white cells can be summarised by saying, that in three-quarters of all the cases there is leucopenia, due to a diminution of the polymorphonuclear cells, the number of lymphocytes being unchanged.

From the pathological point of view it seems clear that the essential feature of the disease is increased blood destruction, rather than a primary disease of the bone marrow. This might be due to a hæmolysin formed by streptococci, but there is no evidence of the disease presenting the usual features of a streptococcal infection. It seems more likely that it is due to

some chemical poison, perhaps a product of protein breakdown under the influence of abnormal bacteria, which have reached the intestine owing to the absence of free hydrochloric acid from the stomach, or produced directly by some unknown, probably protozoal, organism.

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TABLE I.—CASES OF ADDISON'S ANÆMIA KNOWN TO HAVE DIED.

No. of Case.	Age at death or when last seen.	Sex.	Duration of symptoms.	Red Cells (Millions) per cub. mm.	Hæmoglobin percentage.	Colour Index.	Leucocytes per cub. mm.	Lymphocytes percentage.	Aniso-cytosis.	Poikilocytosis.	Nucl. Reds.	Megaloblasts.	Polychromasia.	Punctate Eosinophilia.	Neurological Symptoms.	Gastro-Intestinal Symptoms.	Oral Sepsis.	Prussian Blue Reaction.	Spleen.	Liver.	Bone Marrow.	
1	63	M	2	0.9	30	1.7	3200	34	+	+	+		+	+	—	—	—	+	K, L, S.	160 gm.	1510 gm.	dark red
2	22	F	1	0.7	10	0.7	2300	62	+	+	+		+	+	—	—	—	+	K, L, S.	120	1100	deep red
3	57	F	1	1.0	30	1.5	2200		+	+	+		+	+	—	—	—	+	L, S.	90	1600	
4	65	M	1	2.8	55	1.0	6800	27	+	+	+		+	+	—	—	—	+	K, L, S.	197	1520	deep red
5	58	M	1	1.8	32	0.9	7500	64	+	+	+		+	+	—	—	—	+	K, L, S.	421	2000	normal colour
6	31	M	1	1.4	32	1.1	4200		+	+	+		+	+	—	—	—	+	K, L, S.	180	1240	red
7	34	M	2	1.3	21	0.8			+	+	+		+	+	—	—	—	+	K, L, S.	320	1900	red
8	54	F	3	1.0	22	1.1	9200	12	+	+	+		+	+	—	—	—	+	K, L, S.	1400	2350	deep red
9	44	F	1	1.8	40	1.1	2000	73	+	+	+		+	+	—	—	—	+	K, L, S.	220	1490	red
10	46	F	1	1.0	30	1.5	2300		+	+	+		+	+	—	—	—	+	K, L, S.	enlarged palpable		not very red
11	60	M	4	1.9	35	0.8	7000	42	+	+	+		+	+	—	—	—	+	K, L, S.			
12	54	M	3	1.2	23	1.0	4000		+	+	+		+	+	—	—	—	+	K, L, S.			
13	31	F	2	1.7	45	1.2	2500	46	+	+	+		+	+	—	—	—	+	K, L, S.			
14	52	F	6	1.5	36	1.2	5500	43	+	+	+		+	+	—	—	—	+	K, L, S.			
15	55	F	1	1.9	41	1.1	3700		+	+	+		+	+	—	—	—	+	K, L, S.			
16	41	M	2	0.6	20	1.6	4000		+	+	+		+	+	—	—	—	+	K, L, S.			
17	31	M	1	1.1	26	1.2	1200	46	+	+	+		+	+	—	—	—	+	K, L, S.			
18	50	M	6	1.7	50	1.5			+	+	+		+	+	—	—	—	+	K, L, S.			
19	53	F	3	2.5	61	1.2	3100	34	+	+	+		+	+	—	—	—	+	K, L, S.	390	palpable 2300	red
20	41	M	1	0.6	18	1.5	5000	28	+	+	+		+	+	—	—	—	+	K, L, S.	enlarged	normal	red
21	28	F	2	1.7	40	1.2	5600		+	+	+		+	+	—	—	—	+	K, L, S.	108	normal size 2200	red
22	29	F	2	3.2	53	0.8	3000	30	+	+	+		+	+	—	—	—	+	K, L, S.	normal size 510	normal size 2200	red not examined
23	48	F	5	1.1	22	1.2	2900		+	+	+		+	+	—	—	—	+	K, L, S.	palpable normal size	normal size	normal
24	60	F	1	2.0	30	0.7	3700	36	+	+	+		+	+	—	—	—	+	K, L, S.	palpable normal size	normal size	normal
25	47	F	1	2.2	45	1.0			+	+	+		+	+	—	—	—	+	K, L, S.	palpable	not palp.	red
26	40	M	2	1.2	25	1.1	2100		+	+	+		+	+	—	—	—	+	K, L, S.	not palp.	palpable 1630	red
27	48	M	2	3.0	70	1.1	4500	28	+	+	+		+	+	—	—	—	+	K, L, S.	not palp.	palpable 1630	red
28	40	F	1	0.6	23	2.0	6500	Increased	+	+	+		+	+	—	—	—	+	K, L, S.	palpable normal size	normal size	normal
29	51	F	4	1.1	36	1.7	7300	26	+	+	+		+	+	—	—	—	+	K, L, S.	palpable	not palp.	red
30	33	F	1	1.6	34	1.1	5500	54	+	+	+		+	+	—	—	—	+	K, L, S.	not palp.	palpable 1630	red
31	58	F	1	1.2	25	1.0	2000	54	+	+	+		+	+	—	—	—	+	K, L, S.	not palp.	palpable 1630	red
32	29	M	6	0.6	14	1.1	2900	55	+	+	+		+	+	—	—	—	+	K, L, S.	not palp.	palpable 1630	red
33	40	F	1	1.0	24	1.2	3400		+	+	+		+	+	—	—	—	+	K, L, S.	not palp.	palpable 1630	red
34	42	M	1	1.2	16	0.7	8000	48	+	+	+		+	+	—	—	—	+	K, L, S.	not palp.	palpable 1630	red
35	44	M	1	1.2	29	1.2	5300	30	+	+	+		+	+	—	—	—	+	K, L, S.	not palp.	palpable 1630	red
36	51	M	1	1.6	29	0.9			+	+	+		+	+	—	—	—	+	K, L, S.	not palp.	palpable 1630	red
37	53	M	2	2.1	25	0.6	7000		+	+	+		+	+	—	—	—	+	K, L, S.	not palp.	palpable 1630	red
38	35	M	2	2.3	47	1.1	3800	41	+	+	+		+	+	—	—	—	+	K, L, S.	not palp.	palpable 1630	red
39	61	M	2	2.0	50	1.2	2100	40	+	+	+		+	+	—	—	—	+	K, L, S.	not palp.	palpable 1630	red
40	43	M	1	1.2	35	1.4	3100	40	+	+	+		+	+	—	—	—	+	K, L, S.	not palp.	palpable 1630	red
41	52	M	1	1.5	41	1.3	3000	37	+	+	+		+	+	—	—	—	+	K, L, S.	not palp.	palpable 1630	red
42	28	F	3	1.5	41	1.3	3000	37	+	+	+		+	+	—	—	—	+	K, L, S.	not palp.	palpable 1630	red
43	31	F	1	1.8	28	0.7			+	+	+		+	+	—	—	—	+	K, L, S.	not palp.	palpable 1630	red

• K, L, S indicate that the Prussian blue reaction was positive in kidney, liver and spleen respectively.

TABLE II.—CASES OF ADDISON'S ANÆMIA PROBABLY DEAD.

No. of case.	Age at death or when last seen.	Sex.	Duration of symptoms.	Red Cells (Millions).	Hæmoglobin percentage.	Colour-index.	Leucocytes.	Lymphocytes percentage.	Aniso-cytosis.	Poikilocytosis.	Nucl. Reels.	Megaloblasts.	Polychromasia.	Punctate basophilia.	Neurological symptoms.	Gastro-intestinal symptoms.	Oral Sepsis.	Prussian Blue Reaction.	Spleen.	Liver.
69	58	F	1	1.7	46	1.4	3900	47	+	+	+	+	+	+	—	D and V	?		palpable	palpable
68	69	M	4	1.1	32	1.5	4800	32	+	+	+	+	+	+	—	D and V	+		palpable	palpable
67	63	M	1	1.3	30	1.6	2900	46	+	+	+	+	+	+	—	D and V	+		palpable	palpable
66	61	M	1	1.4	32	1.5	3700	28	+	+	+	+	+	+	—	D and V	+		palpable	palpable
65	64	M	6	1.9	30	0.8	5000	(1910) (1912)	+	+	+	+	+	+	—	D and V	+		palpable	palpable
64	47	M	4	1.4	42	1.5	5000	28	+	+	+	+	+	+	—	D and V	+		palpable	palpable
63	33	M	4	1.8	35	0.7	3700	—	+	+	+	+	+	+	—	D and V	+		palpable	palpable
62	36	M	2	1.8	34	0.9	3700	—	+	+	+	+	+	+	—	D and V	+		palpable	palpable
61	31	M	3	1.8	34	0.8	6000	—	+	+	+	+	+	+	—	D and V	+		palpable	palpable
60	47	F	1	1.7	32	1.3	5000	28	+	+	+	+	+	+	—	D and V	+		palpable	palpable
59	40	M	4	1.7	40	1.2	2800	61	+	+	+	+	+	+	—	D and V	+		palpable	palpable
58	43	M	4	2.0	46	1.1	4600	46	+	+	+	+	+	+	—	D and V	+		palpable	palpable
57	55	M	4	1.8	40	1.1	2700	46	+	+	+	+	+	+	—	D and V	+		palpable	palpable
56	53	M	4	1.8	40	1.1	4600	46	+	+	+	+	+	+	—	D and V	+		palpable	palpable
55	54	M	4	1.8	40	1.1	3000	28	+	+	+	+	+	+	—	D and V	+		palpable	palpable
54	65	M	4	1.8	40	1.1	3000	28	+	+	+	+	+	+	—	D and V	+		palpable	palpable
53	55	M	4	1.7	46	1.1	5500	30	+	+	+	+	+	+	—	D and V	+		palpable	palpable

TABLE III.—CASES OF ADDISON'S ANÆMIA ALIVE 1922.

No. of case.	Age.	Sex.	Duration of symptoms.	Red Cells (Millions).	Hæmoglobin percentage.	Colour-index.	Leucocytes.	Lymphocytes percentage.	Aniso-cytosis.	Poikilocytosis.	Nucl. Reels.	Megaloblasts.	Polychromasia.	Punctate basophilia.	Neurological symptoms.	Gastro-intestinal symptoms.	Oral Sepsis.	Prussian Blue Reaction.	Spleen.	Liver.
81	73	M	2	2.3	25	1.1	6900	28	+	+	+	+	+	+	—	D and V	+		not palp.	palpable
82	51	M	1	3.1	45	0.75	7800	70	+	+	+	+	+	+	—	D and V	+		not palp.	palpable
83	39	M	1	1.0	25	1.2	3100	48	+	+	+	+	+	+	—	D and V	+		not palp.	palpable
84	43	M	3	0.9	38	2.3	1600	43	+	+	+	+	+	+	—	D and V	+		not palp.	palpable
85	43	M	4	1.9	25	0.6	9000	48	+	+	+	+	+	+	—	D and V	+		not palp.	palpable
86	27	F	2	1.2	53	1.4	2800	50	+	+	+	+	+	+	—	D and V	+		not palp.	palpable
87	62	M	1	1.5	20	0.7	4500	—	+	+	+	+	+	+	—	D and V	+		not palp.	palpable
88	55	F	5	1.4	27	1.3	5900	30	+	+	+	+	+	+	—	D and V	+		just palp.	palpable
89	20	M	1	1.4	31	1.3	3100	51	+	+	+	+	+	+	—	D and V	+		just palp.	palpable
90	53	F	6	2.2	56	1.3	4500	45	+	+	+	+	+	+	—	D and V	+		not palp.	palpable
91	56	F	7	1.6	46	1.5	4300	45	+	+	+	+	+	+	—	D and V	+		not palp.	palpable
92	42	F	1	3.0	46	0.7	5800	24	+	+	+	+	+	+	—	D and V	+		not palp.	palpable
93	35	F	3	1.0	20	1.0	3300	20	+	+	+	+	+	+	—	D and V	+		not palp.	palpable
94	35	F	3	1.3	12	1.6	3700	32	+	+	+	+	+	+	—	D and V	+		not palp.	palpable
95	64	F	9	3.2	36	0.6	8500	—	+	+	+	+	+	+	—	D and V	+		not palp.	palpable



TABLE IV. - DOUBTFUL CASES OF ANÆMIA.

No. of Case.	Age.	Sex.	Duration of Symptoms.	Red Cells (millions).	Hæmoglobin percentage.	Colour Index.	Leucocytes.	Lymphocytes percentage.	Aniso-cytosis.	Poikilocytosis.	Nucl. Reds.	Megaloblasts.	Polychro-masia.	Punctate Basophilia.	Neurological Symptoms.	Gastro-intestinal Symptoms.	Oral Sepsis.	Prussian Blue Reaction.	Spleen.	Liver.	Bone Marrow.
101	61	M	7½	1.5	44	1.5	3200	65	+	+	+	—	+	+	?	—	+	+	K, L, S —		

✖ ? aplastic anæmia.  
 oral sepsis cured.  
 ✖ broncho-pneumonia.  
 hæmatemesis, menorrhagia.  
 Wassermann +  
 ✖ purpura ? uterine sepsis.  
 ✖ occult blood in feces.  
 ✖ eosinophilia.  
 Wassermann positive.  
 ? Addison's disease.

TABLE V. - CASES DEFINITELY NOT ADDISON'S ANÆMIA.

No. of Case.	Age 1922 or at death.	Sex.	Duration of Symptoms.	Red Cells (millions).	Hæmoglobin percentage.	Colour Index.	Leucocytes.	Lymphocytes percentage.	Aniso-cytosis.	Poikilocytosis.	Nucl. Reds.	Megaloblasts.	Polychromasia.	Punctate Basophilia.	Neurological Symptoms.	Gastro-intestinal Symptoms.	Oral Sepsis.	Prussian Blue Reaction.	Spleen.	Liver.	Bone Marrow.
111	67	M	5	1.9	35	0.9	11000		+	+	+	(+)	+		-		+	+	not palp.		piles, op. 1919. Anæmia cured. macrocytic. Anæmia (secondary). *suppurative nephritis.
112	61	F	16	2.0	16	0.4	2500	332		+	(+)	-	+		-		+	-	not palp.		*lymphatic leukemia.
113	33	M	24	1.0	23	1.1	2300	47	+	+	(+)	-	+	+	-		+	L, S	430	redder than normal	
114	27	M	6	1.0	28	1.4	16000	80			(+)	-	+	+	-		+	L	enlarged		*myxœdema.
115	52	M	7	4.5	56	0.8	8000	45	(+)	+	(+)	-	+		-		+	K, L, S	not palp.		anæmia due to hæmorrhoids, cured.
116	49	M	14½	2.9	40	0.7	4000	26	+	+	(+)	-	+		-		+	K, L, S	not palp.		*lymphatic leukemia.
117	8	M	7½	1.2	28	1.2	3500					-	+		-		+	L, S	149		*lymphatic leukemia.
118	15	M	4½	1.1	30	1.2	3000	74	+	+	(+)	-	+		-		+	L	183	red	*septicæmia.

piles, opn. 1919. Anæmia cured.  
 hæmorrhoids. Anæmia  
 (? secondary).  
 ✖ suppurative nephritis.  
 ✖ lymphatic leukaemia.  
 ✖ myxœdema.  
 anæmia due to hæmorrhoids;  
 cured.  
 ✖ lymphatic leukaemia.  
 ✖ septicæmia.

## APPENDIX B

CASES ILLUSTRATING SPECIAL POINTS IN THE  
PREVIOUS DISCUSSION*Case of Addison's Anæmia in a Young Woman (No. 2)*

May B., aged 22, was admitted under Dr. Newton Pitt in December 1913. A year before she became pale and weak. Her teeth were all removed, and she lost a lot of blood after this. Her periods had always been irregular; latterly she had lost an unusual amount of blood; there was three weeks' history of vomiting. On admission she was said to be a greenish colour. There were petechiæ on the skin and retinal hæmorrhages. A blood count showed red cells 700,000, hæmoglobin 10 per cent., colour-index 0·7, white cells 2300, of which 62 per cent. were lymphocytes. There was marked aniso- and poikilo-cytosis, but no nucleated red cells. Her temperature was between 100° and 101°. She died three days after admission.

Post-mortem, there were hæmorrhages throughout the intestine, in the lungs and pericardium. The Prussian blue reaction was positive in the liver and weakly positive in the spleen and kidneys. The bone marrow of the femur was deep red. A cultivation from the heart blood grew *B. coli*, but this may well have been a terminal infection.

*Case of Addison's Anæmia in a Young Woman with Changes in the Spinal Cord (No. 13)*

Amy G., aged 31, was admitted under Sir William Hale-White in October 1909. She had been growing weaker for two years. On admission she was very pale, and a blood examination showed red cells 1·7 millions, hæmoglobin 45 per cent., colour-index 1·2, and white cells 2500. Unfortunately a blood film was not examined. She had no vomiting or diarrhœa, but had had epigastric pain since the beginning of her illness. Her temperature was between 101° and 104° during the ten days that she was in hospital before her death. The knee jerks were exaggerated and the plantar reflexes were extensor.

Post-mortem the liver, spleen and kidneys gave a positive Prussian blue reaction. The bone marrow of the femur was red. Sections of the cord showed degeneration of the posterior and lateral columns.

*Case of Addison's Anæmia occurring in a Worker with Radium (No. 17)*

Leonard H., aged 31, was admitted under Sir William Hale-White in October 1916. He had worked at a radium institute for four years. For one month before admission he had complained of weakness, shortness of breath and headaches. There were no special gastro-intestinal or neurological symptoms. He was sallow-coloured and had a temperature of 103° on three

occasions while he was in hospital. A blood count showed red cells 1·3 millions, hæmoglobin 29 per cent., colour-index 1·1 and white cells 960, of which 48 per cent. were lymphocytes. There was poikilo- and aniso-cytosis. Nucleated red cells were not mentioned as present. A second blood count a fortnight later showed little change. He died a few weeks after discharge. Unfortunately a post-mortem examination was not made.

*Case of Addison's Anæmia and Phthisis simulating Addison's Disease (No. 35)*

Fred P., aged 42, was admitted into Clinical Ward in May 1911. He had suffered with a cough for ten years following an attack of pleurisy. Six months before admission he became pale and weak and had loss of power in the legs. On admission, although he had not been treated with arsenic, he had brown spots of pigmentation over the body and limbs and large blotches on the abdomen. He had also pigmentation of the mucous membrane of the lips and cheeks and leucodermia.

His spleen was not palpable. He had attacks of diarrhœa but no vomiting. His right knee jerk was exaggerated. There was ankle clonus and a doubtful extensor plantar reflex. His blood pressure on admission was 120 mm., but in October it was constantly about 90 mm., and was unaffected by adrenalin given by the mouth. A blood count gave the following result : red cells 1·2 millions, hæmoglobin 29 per cent., colour-index 1·2, and white cells 5300, of which 30 per cent. were lymphocytes. There was aniso- and poikilo-cytosis, basophil staining and nucleated red cells.

In June the signs in his R. lung became more active. There were râles all over and a rub developed at the R. base. Later tubercle bacilli were found in the sputum. In August he had diarrhœa and vomiting and peripheral neuritis, and arsenic was omitted. He was intermittently pyrexial, and became worse and died in October.

Post-mortem there was an old cavity at the R. apex and tuberculosis of both lungs. The liver was enlarged and there was a well-marked Prussian blue reaction in the liver, spleen and kidneys. The bone marrow was bright red.

*Case of Addison's Anæmia associated with Infective Arthritis (No. 42)*

Daisy W., aged 26, was admitted under Dr. Fawcett in August 1917. She was married in June 1916, and soon after this suffered with bilious attacks and anæmia. On admission she was a lemon-yellow colour and a blood count showed red cells 1·5 millions, hæmoglobin 28 per cent., colour-index 0·9, and white cells 7000 (later 3000), of which 55 per cent. were lymphocytes. There was marked aniso- and poikilo-cytosis and nucleated red cells were present. In hospital the vomiting continued, and there were slight attacks of diarrhœa, which did

not appear to be due to arsenic. She had had no child or miscarriage, and her periods were regular but rather excessive. She had low pyrexia throughout her stay in hospital, sometimes to 102°, but her spleen was not palpable. She was discharged after four months considerably improved, but with her hæmoglobin still 40 per cent.

In May 1918 she was readmitted with infective arthritis of rheumatoid distribution, and peripheral neuritis. Her anæmia was apparently not severe.

In November 1918 she was readmitted, as her arthritis and peripheral neuritis were worse. The latter was thought to be due to arsenic, and this was detected in the urine. Her hæmoglobin was 90 per cent., but while in hospital it fell steadily, perhaps because her arsenic had to be discontinued, until in February 1919 it was again 36 per cent. She was discharged but died at home in June 1919.

*Case of Addison's Anæmia with Remissions during eight years*  
(No. 83)

George C., aged 39, was admitted under Dr. Fawcett in March 1920. In 1912 he first noticed that he was inclined to be yellow. In 1913 he was in bed for a month with weakness and a yellow colour. In 1914 he was very ill while in Mexico, and evidently had considerable pyrexia in addition to his yellow colour, diarrhoea and vomiting, for he was diagnosed as a case of Addison's anæmia and typhoid fever. In 1915 he was in Norwood Cottage Hospital and was treated with injections of salvarsan. He was able to work till March 1916, the longest remission he had had since 1913. From that date till his admission he was never well for more than a few months at a time. He had frequent attacks of diarrhoea and vomiting, some of which may have been due to arsenic, as he was generally under treatment with arsenic by the mouth or by injections.

On admission he was a lemon-yellow colour and had severe anæmia. His spleen was palpable about an inch below the costal margin, and his liver was just palpable. A blood count showed red cells 1·2 millions, hæmoglobin 28 per cent., colour-index 1·2, and white cells 1600, of which 43 per cent. were lymphocytes. There was aniso- and poikilo-cytosis, and normoblasts and megaloblasts were present. The fragility of his red cells was normal. His clotting time was 2' 25". A fractional test-meal showed achlorhydria. His Wassermann reaction was negative on several occasions. Early in May he developed a subacute attack of nephritis which persisted. For the first two months in hospital there was no improvement in his general condition and no increase in his hæmoglobin percentage. He was then transfused on May 22, May 31 and June 16, about 500 c.c. of blood being used on each occasion. After the first two transfusions he only managed to keep at about the figure produced immediately after the transfusion, but after the third he rose rapidly from 40 per cent. to 72 per

cent. He was discharged feeling very fit and returned to work. In October his hæmoglobin was 88 per cent. In May 1921 his hæmoglobin was 83 per cent., but a fractional test-meal still showed complete achlorhydria. He remained well and at work till January 1922—the longest interval of good health since 1913.

In January he became acutely ill, and rapidly lost his colour, and was admitted to hospital with jaundice and acute abdominal pain over the gall bladder. Cholecystitis and an acute hæmolytic phase were diagnosed. His hæmoglobin was down to 24 per cent. He was again treated with arsenic and transfusions, and although his hæmoglobin was gradually raised to 54 per cent., he did not regain his strength. He was transferred to Mr. Fagge in June 1922. At a laparotomy his gall bladder was found to be the site of chronic inflammatory changes, and was removed. It contained thick inspissated bile, almost firm enough to be described as small stones. A pure culture of *B. coli* was grown from the gall bladder. He made an uneventful recovery from the operation and seems to be going on well.

*Case of Addison's Anæmia, cured four years later (No. 91)*

Evelyn R., aged 49, a married woman with nine children, was admitted under Dr. Fawcett in May 1918. For four years she had been getting weak, and two years before admission she had an attack of abdominal pain and vomiting which was diagnosed gastritis. She noticed that she was rather yellow. About this time, and for some years previously, she had had small ulcers in the mouth whenever she got run down. Nine months before admission she had again nausea and vomiting and her weakness became worse. She was constipated, and at no time had diarrhœa except when she was being treated with large doses of arsenic.

On admission she was lemon-yellow, and had a moderately severe anæmia. A count by Dr. Nicholson showed red cells 1·6 millions, hæmoglobin 46 per cent., colour-index 1·5, and white cells 4300, of which 45 per cent. were lymphocytes. There was marked poikilo- and aniso-cytosis with polychromasia and punctate basophilia. Nucleated red cells, but no megaloblasts, were present. Her spleen was not palpable and there were no neurological symptoms. Her mouth was clean, as all her carious teeth had been extracted in 1917. Her temperature varied between 100° and 101° for two or three weeks after admission. She was treated with a dozen injections of iron cacodylate and arsenic by the mouth in increasing doses, continued about a month after her discharge from hospital. She was discharged after four months in hospital much improved, with a hæmoglobin percentage of 65. She continued to improve, and five months later was able to return to her full household duties, and four years later, when we saw her, she had had no relapse. Her hæmoglobin percentage was 82, her blood film was normal, and she seemed in perfect health. Although she

never suffered from diarrhœa, and had no trouble of any sort with her digestion, a fractional test-meal showed complete achlorhydria, without rapid emptying.

There does not seem to be any doubt about the diagnosis, but four years of good health is not quite so sure a proof of cure as in No. 98, where there were seven years of good health. It is interesting that of these two, one had achlorhydria, and the other had a normal test-meal.

*Case of Addison's Anæmia in good health seven years later  
(No. 98)*

Ellen K., aged 35, was admitted under Dr. Fawcett in August 1915. In November 1914 her fifth child was born. The confinement was normal, but there was a discharge for six weeks afterwards, which was more than on other occasions. In March 1915 she became a yellow colour, lost her appetite and was very weak. This continued until admission. Her appetite became worse, she had constant nausea but only vomited once. There was no diarrhœa. Fortunately three blood examinations were made by Dr. Nicholson. The first showed red cells one million, hæmoglobin 20 per cent., colour-index 1·0, and white cells 3900, of which 20 per cent. were lymphocytes. There was marked aniso-cytosis, poikilo-cytosis and basophil staining. Fifteen normoblasts were counted among 500 cells. The other blood counts gave a similar picture, but the hæmoglobin gradually increased to 50 per cent. Excess of urobilin was present in the urine. There was low pyrexia at the beginning of her stay in hospital. Unfortunately a test-meal was not done, there was no note about the size of the spleen, and megaloblasts were not seen in the three films examined. Both from the clinical point of view and from the blood picture there was no reason to question the diagnosis at that time. The picture was much more complete than in many other cases, where a post-mortem examination proved that the diagnosis was correct.

She was treated with arsenic in increasing doses for about five months. She was six weeks in hospital, during which time her hæmoglobin rose to 50 per cent. A month after her discharge she felt quite well, and for the next eight years, until seen in 1922, she remained absolutely well and was able to do all her ordinary household work. In 1919 she had a seven-months baby who did not live long. She had a severe hæmorrhage but no return of her anæmia or yellow colour. The same year during the epidemic she had an attack of influenza, from which she recovered normally. We saw her in March 1922, and could find no signs of disease. Her red cells were 4·5 millions, her hæmoglobin 84 per cent. and the white count 7600. A blood film was normal. A fractional test-meal showed no free acid in the first three specimens, but afterwards a normal curve. She still had five septic roots with marked pyorrhœa exactly as noted in 1915. All her other teeth had fallen out in 1897.

*Case of Addison's Anæmia apparently associated with  
Suppuration of the Frontal Sinus (No. 94)*

Elsie L., aged 32, was admitted under Dr. Beddard in October 1919. In December 1916 she had an operation for disease of the frontal sinus, which had troubled her for many years. For two years she had had diarrhœa, and for one year attacks of vomiting. Her teeth were good, but she had frequently had aphthous ulcers of the mouth. There was low pyrexia, the spleen was not palpable and there were no neurological symptoms. A blood count showed red cells 1·8 millions, hæmoglobin 42 per cent., colour-index 1·6, and white cells 3700, of which 32 per cent. were lymphocytes. There was marked aniso- and poikilo-cytosis and basophil staining. Normoblasts and megaloblasts were present. She was treated with arsenic and blood transfusions, and a further operation to deal with the sepsis from her frontal sinus, and improved considerably, her hæmoglobin rising to 80 per cent.

Two years later we were unfortunately unable to see her, but heard that she still had anæmia and had needed further blood transfusions, and had been in bed for eighteen months. In May 1922, after a three-months' course of vigorous treatment, she wrote that she was better than she had been for years and hoped that she was cured.

*Case of Anæmia and Suppurative Nephritis with some Post-mortem Changes and Blood Count typical of Addison's Anæmia  
(No. 118)*

Rupert E., aged 31, was admitted under Sir William Hale-White in June 1916. Six months previously after an illness which was diagnosed "influenza" he became anæmic. On admission he had a slight yellow colour, a severe anæmia with little change in the nature of the red blood cells, and blood and albumen in the urine. His liver and spleen were not palpable. He had no neurological or gastro-intestinal symptoms and his test-meal was normal. He was discharged three months later without a very great improvement in his hæmoglobin, still passing large quantities of blood in his urine. His gums had also bled on four occasions since the beginning of his illness, once for two days.

In April 1917 he was readmitted for more acute symptoms, following an exacerbation of his hæmaturia. His urine contained blood albumen and cylindrical casts, and *Staph. albus* was cultivated from it.

In June 1918 he was again admitted, and died two months later. His blood counts were as follows:—

	Red cells (millions).	Hæmo- globin.	Colour- index.	White cells.	Aniso- cytosis.	Poikilo- cytosis.	Nucleated red cells.	Megalo- blasts.	Lymphocytes.
16.6.16.	1·6	30	0·9	3400	(+)	—	—	—	21 <sup>0</sup> / <sub>0</sub>
24.8.16.	1·2	38	1·7	2600	++	++	—	—	39 <sup>0</sup> / <sub>0</sub>
22.9.16.	1·9	44	1·2	2600	+	+	+	—	32 <sup>0</sup> / <sub>0</sub>
24.4.17.	1·0	23	1·1	2300	...	+	+	—	47 <sup>0</sup> / <sub>0</sub>
1.6.17.	1·5	21	0·9	—	.	.	.	.	.

Post-mortem the lungs were œdematous, there were 30 oz. of fluid in the left side of the chest and 16 oz. of fluid in the pericardium. The liver did not give Peil's test. There was recent endocarditis of the mitral valve and infarcts in the spleen. The kidneys contained multiple abscesses and gave a marked Prussian blue reaction.

*Case of Leucanæmia (No. 114)*

Will. V., aged 27, was admitted in April 1910 under Dr. Beddard. Five years before the glands in his neck enlarged and gradually the glands in the groins and axillæ also enlarged. For two years he had been anæmic. On admission he was a yellowish colour, and in addition to the enlarged glands, his spleen could be felt two inches below the costal margin. In May his hæmoglobin was 50 per cent. In June a blood count by Dr. Price Jones gave the following result—red cells one million, hæmoglobin 28 per cent., colour-index 1·4, and white cells 16,000, of which 80 per cent. were lymphocytes. One nucleated red cell was seen. Before his death in July the white cells were said to have risen to 177,000, of which over 90 per cent. were lymphocytes. There were no gastro-intestinal or neurological symptoms.

Post-mortem there was general enlargement of the lymphatic glands, including the mediastinal and mesenteric glands. The bone marrow was red and the heart showed tabby-cat striation. The liver and spleen (430 grms.) gave a marked Prussian blue reaction. The kidneys were normal.

*Case of Anæmia and Myxœdema with some Post-mortem Changes of Addison's Anæmia (No. 115)*

Charles F., aged 52, was admitted under Dr. Fawcett in November 1920. He had suffered intermittently for seven years with weakness, malaise and loss of weight. During this time, and especially during the last four years, he had exceptionally severe pyorrhœa alveolaris. On admission his general appearance and behaviour were characteristic of myxœdema, and this was confirmed by a greatly reduced basal metabolism.

He was anæmic-looking, and several blood examinations were made. The red cells were 4·5 millions per c.mm., the hæmoglobin varied from 56 to 59, and the colour-index from 0·7 to 0·8. His white cells were about 7–8000 and lymphocytes varied from 42 to 55 per cent. There was slight aniso-cytosis, no poikilo-cytosis, no basophil staining and no nucleated red cells. The liver and spleen were not palpable. There were no neurological or gastro-intestinal symptoms. The test-meal showed achlorhydria for the first hour with a subsequent rise to the normal figures. The knee and ankle jerks were absent and there was constantly doubt about whether the plantar reflexes were really extensor. After improving for a month



on thyroid extract and after the removal of his teeth, he developed a septic throat, conjunctivitis and otitis media. *Staph. aureus* was grown from the throat, the eye and the ear. His fever persisted for ten days till his death.

Post-mortem the thyroid was small and fibrotic. The liver gave a marked Prussian blue reaction. Unfortunately the spinal cord and bone marrow were not examined.

*Case of Septicæmia with Post-mortem Changes typical of Addison's Anæmia (No. 117)*

Alfred B., aged 8, was admitted under Dr. Newton Pitt in March 1913. Four months previously he had started with an acute febrile illness with pains in the joints. In hospital his temperature generally reached 104° in the evening. His colour was yellowish. There were no neurological or gastro-intestinal symptoms. The average of two blood counts was red cells 1·2 millions, hæmoglobin 28 per cent., white cells 3500, and colour-index 1·2. A blood film was not examined. He died ten days after admission.

Post-mortem the liver gave a strongly positive, and the spleen and kidneys a slightly positive Prussian blue reaction. The bone marrow of the tibia was bright red. The fat was a deep yellow colour and the heart showed "tabby-cat" striation. A blood culture taken post-mortem grew *Strept. longus* and *Staph. aureus*.

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## NOTES ON A CONSECUTIVE SERIES OF 425 GASTRIC ANALYSES BY THE FRACTIONAL METHOD

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THERE are many fallacies to be guarded against in the fractional method of gastric analysis, both in the technique and in the interpretation of the results. The fact that various observers have carried out the tests in this series prevents the results obtained being strictly uniform, but the margin of error in over 400 analyses must be very small.

The diagnoses are a further unavoidable source of error, which I have endeavoured to minimise by carefully excluding all cases which did not reach a high standard of probability, and distinguishing these with a prefixed query.

Thus while taking every precaution to make this classification as reliable as possible, I realise that both the classification and the conclusions drawn are merely tentative, and I bring them forward with these reservations in the hope that they may be of some interest.

The series consists of 243 analyses made on Dr. A. F. Hurst's private patients at New Lodge Clinic, Windsor Forest, during the period February 1921 to March 1922 inclusive, and 182 analyses made at Guy's Hospital on patients in Addison and Mary wards under Dr. A. F. Hurst and Dr. G. H. Hunt during 1920 and 1921, and on various out-patients. It thus embraces both private and hospital patients and bed and walking cases.

The series is a consecutive one and does not represent especially selected cases. They were of great variety: all were admitted for medical diseases, but not all had gastric symptoms. In the majority the diagnoses were made on clinical grounds, and on evidence afforded by various special investigations, those confirmed by operation or autopsy being greatly in the minority.

A purely arbitrary method of classification has been adopted, based upon a comparison between the free hydrochloric acid

curves with the area plotted by Bennett and Ryle<sup>1</sup> to contain the curves of 80 per cent. of normal people (Fig. 1).

Almost every curve could be easily placed into one of the following groups—

I. *Achlorhydria*, in which free hydrochloric acid, as determined by dimethylamidoazobenzene indicator, is present at no period of the analysis.

I am aware that this interpretation of achlorhydria as a true achlorhydria is open to criticism, but no other indicator

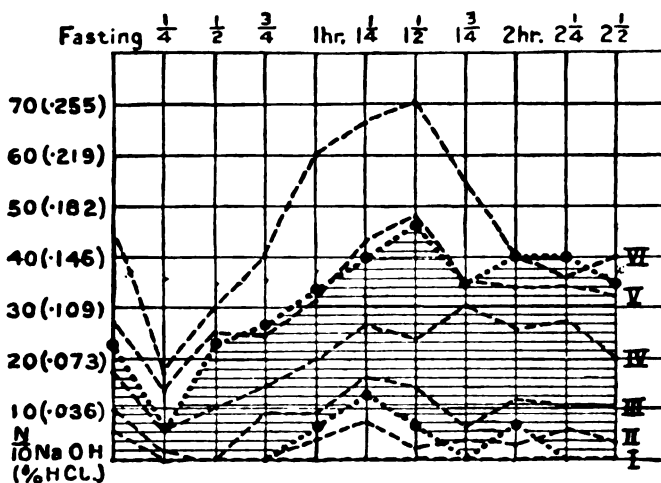


FIG. 1.

The shaded area represents the limits of free HCl (dimethyl indicator), in 80 per cent. of normal people.

----- represents free HCl.

The method of classification of curves adopted, as illustrated by average examples of each, I, II, III, etc., refer to the types as detailed in the text.

was used in the great majority of the titrations, and the term is used here purely as defined above.

II. *Hypochlorhydria*, in which the curve has not exceeded the 10 unit (0.036 per cent. HCl) line.

III. *Low Normal*, in which the curve follows the lower limit of the 80 per cent. normal area. Many of these are closely allied to the hypochlorhydria group, but on the whole it was considered advisable to separate them.

IV. *Normal*, corresponding to the central zone in which Bennett and Ryle found 50 per cent. of the curves of normal people.

V. *High Normal*, in which the curves approximated to the upper limit of the 80 per cent. normal area, and even exceeded

it somewhat, thus reserving for the last group undoubted cases of hyperchlorhydria.

VI. *Hyperchlorhydria*, in none of which was the free HCl lower than 60 units (0.219 per cent. HCl) at one or more periods of the analysis.

Doubtful cases of hyperchlorhydria have been included with the high normals.

This method of classification would be misleading had not one person interpreted the whole series in a uniform manner.

TABLE I

The series classified under the six headings, with reference to age and sex. Six cases of over seventy years of age are included in the last decade. No children under ten years old were examined.

Age Decades.	Achlorhydria.		Hypochlorhydria.		Low Normal.		Normal.		High Normal.		Hyperchlorhydria	
	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.
11-20	0	0	0	0	0	1	2	3	0	0	0	0
21-30	3	4	1	3	5	7	9	15	1	7	12	3
31-40	5	9	7	8	6	4	16	13	10	6	12	15
41-50	12	10	6	13	5	8	15	19	12	3	17	4
51-60	5	7	8	3	2	7	12	4	6	1	20	6
61-74	7	1	2	2	0	1	4	0	0	1	10	5
Total	32	31	24	29	18	28	58	54	29	18	71	33
	63		53		46		112		47		104	

Table I shows the age incidence in decades of the various curves. Through the courtesy of Dr. T. Izod Bennett and Dr. J. A. Ryle, I have had access to the protocols of the 100 normal students, whose gastric secretion they investigated. I have classified them in the same manner as the present series, thus obtaining an interesting comparison, which is seen in Table II.

TABLE II

A percentage comparison between the present series and the series of 100 normal people examined by Bennett and Ryle, both being classified in the manner described.

	Achlor- hydria.	Hypochlor- hydria.	Low Normal.	Normal.	High Normal.	Hyperchlor- hydria.
"Normals" (Bennett and Ryle)	4 %	1 %	10 %	59 %	18 %	8 %
Present Series	14.8 %	12.5 %	10.8 %	26.4 %	11.1 %	24.4 %

This shows, as would be expected, that the percentage falling within normal limits is much lower in the present series, and that the deficit is mainly due to the greatly increased

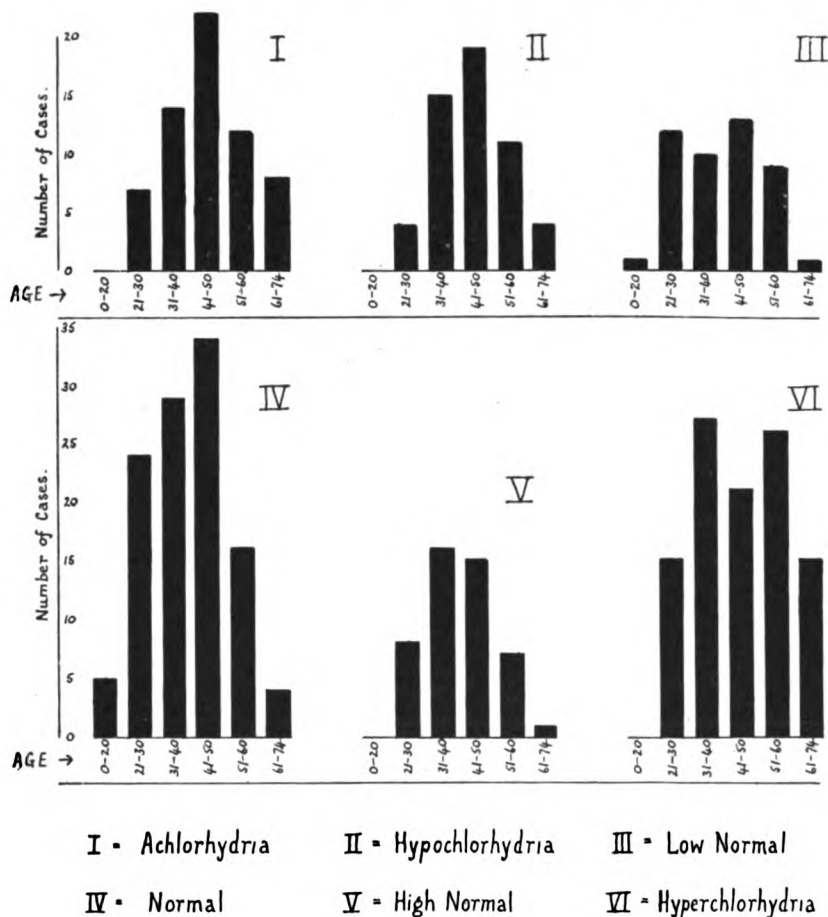


FIG. 2.

A diagrammatic representation of the relative number of cases in the various age decades, grouped under the six headings.

number of cases with extremely low curves. Thus, combining the achlorhydrias with the hypochlorhydrias, there are 27.3 per cent. contrasted with 5 per cent. in the normal series.

The next point is shown more clearly by Fig. 2, in which it will be seen that hyperchlorhydria is relatively much more frequent after the middle decade (41-50), as compared with the decade incidence of the other types.

This is of interest, and definitely disproves the prevalent idea that the acidity of the gastric secretion tends to become less with advancing age. Haneborg,<sup>2</sup> of Christiania, in his monograph on *The Effects of Alcohol upon Digestion in the Stomach*, is one of the most recent writers who subscribe to this view.

Actually there were 62 cases of hyperchlorhydria in patients over forty years of age, as compared with 42 cases under forty years, and no fewer than 20 were of sixty years and upwards.

With regard to sex, it will be seen that in the series there were 232 males and 193 females. In order to reduce these figures to a common standard for purposes of comparison, the number of female cases is multiplied by the factor 1.2, and the result shown in Table III is obtained.

TABLE III

A comparison between the sexes of the various types of curves, with reference to the number of cases, percentage incidence, and average age of each group.

Type of Curve.	Males.				Females.			
	Number.	% of Total Males.	Average Age.	Total Average Age.	Number.	% of Total Females.	Average Age.	Total Average Age.
Achlorhydria .	32	13.8	52.0	45.2	37.2	16.1	43.9	40.1
Hypochlorhydria .	24	10.3	46.5		34.8	15.0	43.7	
Low normal .	18	7.7	39.1		33.6	14.5	41.7	
Normal .	58	25.1	42.0		64.8	28.0	35.8	
High normal .	29	12.5	42.9		21.6	9.3	34.8	
Hyperchlorhydria .	71	30.6	47.0		39.6	17.1	43.9	

Thus it would appear that women preponderated over men in the lower curves (excluding achlorhydria) by 68.4 to 42, and men over women in the higher curves by 100 to 61.2.

This is of considerable importance in interpreting the curves of the two sexes, a moderate degree of hyperchlorhydria in a woman, for example, being more noteworthy than the same degree in a man.

Fig. 3 brings out the difference more clearly.

Tabulating the various diagnoses under the six types of curves, and bearing in mind that those preceded by a query are open to doubt, and merely represent the most probable diagnosis, it is possible to draw up Table IV.

# FRACTIONAL GASTRIC ANALYSIS 307

Where more than one disease was present, that most likely to influence the gastric secretion is mentioned; in cases where this could not be done with reasonable probability, the diseases are included under separate headings.

Diseases with a total number less than 4 are not included, unless of peculiar interest.

TABLE IV

Detailed classification of the curves of gastric acidity in various diseases.

Diagnosis.	Number of Cases.	Achlor-hydræ.	Hypochlor-hydræ.	Low Normal.	Normal.	High Normal.	Hyperchlor-hydræ
<i>Alimentary System :</i>							
Chronic Gastritis . . . . .							
(including Alcoholic)	11	5	2	1	0	2	1
Gastric Ulcer . . . . .	24	1	3	4	5	6	5
? Gastric Ulcer . . . . .	18	1	2	3	1	5	6
Carcinoma of Stomach . . . . .	10	3	3	2	1	1	0
? Carcinoma of Stomach . . . . .	3	2	0	1	0	0	0
Duodenal Ulcer . . . . .	34	0	0	4	3	9	18
? Duodenal Ulcer . . . . .	10	1	0	1	3	1	4
Nervous Dyspepsia . . . . .	37	2	4	3	10	3	15
Gastro-jejuno-stomy							
sequelæ . . . . .	22	4	4	5	4	1	4
Hysterical Vomiting . . . . .	6	0	1	1	3	1	0
Gallstones . . . . .	7	1	0	0	4	1	1
Cirrhosis of Liver . . . . .	3	1	0	0	1	0	1
Carcinoma of Pancreas . . . . .	2	2	0	0	0	0	0
? Carcinoma of Pancreas . . . . .	2	2	0	0	0	0	0
Chronic Pancreatitis . . . . .	1	1	0	0	0	0	0
Carcinoma of Colon . . . . .	3	0	0	0	0	1	2
? Carcinoma of Colon . . . . .	2	1	0	0	1	0	0
Chronic Colitis . . . . .	11	0	2	2	4	3	0
Ulcerative Colitis . . . . .	3	0	0	0	1	1	1
Enterospasm . . . . .	4	0	0	0	3	0	1
Visceroptosis . . . . .							
(including Gastrop-tosis)	19	2	5	5	3	0	4
Chronic Appendicitis . . . . .	13	3	0	1	5	1	3
Constipation . . . . .	12	1	1	1	7	1	1
Diarrhœa . . . . .	4	1	0	1	2	0	0
<i>Indiscriminate :</i>							
<i>Addison's (Pernicious)</i>							
Anæmia . . . . .	6	6	0	0	0	0	0
Secondary Anæmia . . . . .	5	2	0	0	3	0	0
Subacute Combined De-							
generation of Cord . . . . .	3	3	0	0	0	0	0
Tubes Dorsalis . . . . .	9	1	1	2	2	1	2
Disseminated Sclerosis . . . . .	8	0	1	1	4	2	0
Rheumatoid Arthritis . . . . .	8	3	1	1	0	0	3
Fibrositis . . . . .	5	2	2	0	0	1	0
Asthma . . . . .	4	1	1	0	0	1	1
Addison's Disease . . . . .	2	1	1	0	0	0	0
Neurasthenia . . . . .	20	2	6	1	5	1	5
Psychasthenia . . . . .	11	1	2	1	5	2	0
Hypochondriasis . . . . .	3	0	0	0	2	0	1

The next table (Table V) represents a comparison by percentages between various diseases selected from Table IV and the normals of Bennett and Ryle.

It requires no elaboration, but perhaps the emphasising of certain points may be of value.

1. *Gastric Ulcer and Duodenal Ulcer.*—In the gastric ulcer cases, males and females were evenly represented, there being 11 of the former and 13 of the latter. The average age was 40·3 years, and there was no definite decade incidence.

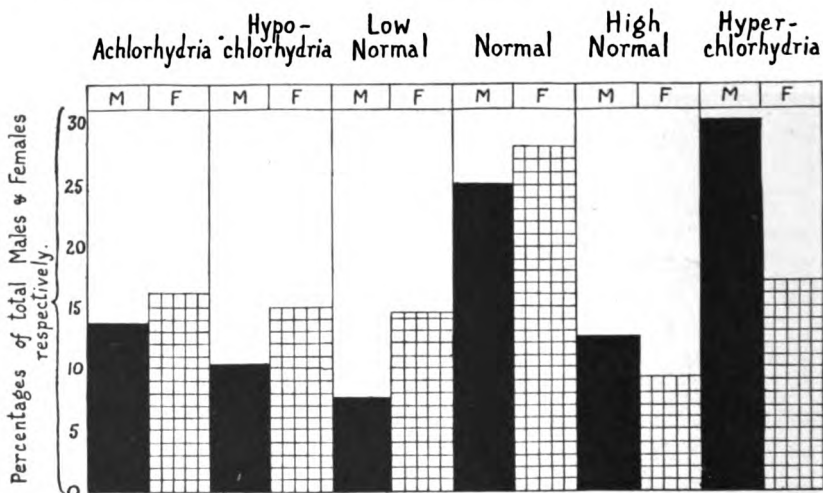


FIG. 3.

Diagram illustrating the relative frequency of low curves of gastric acidity in women as compared with men, and the relative frequency of high curves in men as compared with women.

In the duodenal ulcer cases males greatly exceeded females, there being 28 of the former and only 6 of the latter, *i. e.* duodenal ulcer was more than four times as frequent in males as in females. The average age was 45·6 years, and it was found that duodenal ulcer was relatively uncommon under thirty years of age.

The decade incidence of the two conditions was as follows—

Decade.	Gastric Ulcer.	Duodenal Ulcer.
1st	0	0
2nd	0	0
3rd	6	4
4th	5	9
5th	8	9
6th	5	9
7th	0	2
8th	0	1



Another point, confirming many recent observations, is the variability of the acidity in gastric ulcer from complete achlorhydria to hyperchlorhydria. This is in marked contrast to the definite tendency to a high curve of acidity in duodenal ulcer.

2. *Gastro-jejunosomy*.—These naturally represent the surgical failures, and this accounts for the relatively high proportion which still have free HCl.

They were complicated with jejunal or gastro-jejunal ulcers, or the symptoms which the operation had sought to relieve were still present, or other symptoms, generally indicative of entero-colic irritation, had developed.

No complications occurring after a gastro-jejunosomy had been performed are included under their respective headings in the classified list.

3. *Chronic Appendicitis*.—Although the total number of cases is very small, it will be seen that some were associated with complete absence of free HCl in the gastric contents, and some with hyperchlorhydria.

Dr. A. F. Hurst has suggested that when the appendicitis is associated with achlorhydria, the former is secondary to the latter, the defensive barrier of the gastric hydrochloric acid being absent, so that infection of the lower alimentary tract is more likely to occur. When the appendicitis is, on the other hand, accompanied by hyperchlorhydria, he believes that the latter may be, like the gastric symptoms of appendix dyspepsia, a reflex manifestation of the former.

4. *Rheumatoid Arthritis*.—A striking proportion of achlorhydria and low curves is seen; this is of considerable interest, although the percentage of hyperchlorhydria cannot be overlooked. The absence or gross deficiency of hydrochloric acid in the gastric juice of those people who have oral sepsis renders them peculiarly liable to intestinal infection, as in the association of appendicitis with achlorhydria.

Thus, in the treatment of such cases of rheumatoid arthritis, the administration of hydrochloric acid is of great importance, in addition to dealing with the oral sepsis and infection of the intestine.

5. *Addison's Anæmia*.—The constancy of the achlorhydria in this small series is in agreement with other recent statistics both published and unpublished. The absence of free hydrochloric acid is shown in an even more striking manner than

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by the old one-hour test meal analysis, for it is constant throughout the whole test, and even the curve of total acidity rarely rises to any appreciable extent above the 10 unit (0.036 per cent. HCl) line. Furthermore, the achlorhydria is a complete one, for there is no reaction to litmus or congo-red indicators.

6. *Carcinoma of Stomach*.—All these cases were proved by operation or post-mortem, and it is very instructive to note the small proportion with absent free HCl, as compared with the constant achlorhydria of Addison's anæmia. This may on occasion prove a useful point in the differential diagnosis of the two conditions.

7. *Disorders of the Pancreas*.—Although the numbers are so small, it surely must be more than mere coincidence that the five cases of carcinoma, probable carcinoma, and chronic inflammation of the pancreas, are without exception associated with achlorhydria. A more recent case, not included in this series, in which the diagnosis of chronic pancreatitis could be confidently made, also showed complete achlorhydria.

TABLE V

A comparison between the percentage incidence of the six types of curves in various diseases, with the normal.

Disease.	Number of Cases.	Percentages.					
		Achlorhydria.	Hypochlorhydria.	Low Normal.	Normal.	High Normal.	Hyperchlorhydria
Normal . . . . . (Bennett and Ryle)	100	4.0	1.0	10.0	59.0	18.0	8.0
Chronic Gastritis . . . . .	11	45.4	18.1	9.0	0	18.1	9.0
Gastric Ulcer . . . . .	24	4.1	12.5	16.6	20.8	25.0	20.8
Carcinoma of Stomach . . . . .	10	30.0	30.0	20.0	10.0	10.0	0
Duodenal Ulcer . . . . .	34	0	0	11.7	8.8	26.4	53.0
Nervous Dyspepsia . . . . .	37	5.4	10.9	8.1	27.0	8.1	40.5
Gastro-jejunostomy sequelæ . . . . .	22	18.1	18.1	22.7	18.1	4.5	18.1
Visceroptosis, including Gastroptosis . . . . .	19	10.5	26.3	26.3	15.7	0	21.0
Gallstones . . . . .	7	14.2	0	0	57.1	14.2	14.2
Chronic Appendicitis . . . . .	13	23.0	0	7.6	38.4	7.6	23.1
Addison's Anæmia . . . . .	6	100.0	0	0	0	0	0
Tabes Dorsalis . . . . .	9	11.1	11.1	22.2	22.2	11.1	22.2
Disseminated Sclerosis . . . . .	8	0	12.5	12.5	50.0	25.0	0
Rheumatoid Arthritis . . . . .	8	37.5	12.5	12.5	0	0	37.5
Neurasthenia . . . . .	20	10.0	30.0	5.0	25.0	5.0	25.0
Psychasthenia . . . . .	11	9.0	18.1	9.0	45.4	18.1	0

TABLE VI

A comparison of certain diseases by the percentages of low, normal, and high curves of gastric acidity. "Low" curves are taken to include achlorhydria, hypochlorhydria, and low normal curves; "high" curves include high normal and hyperchlorhydria curves.

Disease.	Percentages.		
	Low.	Normal.	High.
Normal . . . . .	15.0	59.0	26.0
Chronic Gastritis . . . . .	72.5	0	27.1
Gastric Ulcer . . . . .	33.2	20.8	45.8
Carcinoma of Stomach . . . . .	80.0	10.0	10.0
Duodenal Ulcer . . . . .	11.7	8.8	79.4
Gastro-jejunostomy sequelæ . . . . .	59.0	18.1	22.6
Chronic Appendicitis . . . . .	30.6	38.4	30.7
Rheumatoid Arthritis . . . . .	62.5	0	37.5

On examining the cases met with under the six headings the following information is obtained—

1. *Achlorhydria Group.*

Males . . . . .	32	Average age . . . . .	52.0
Females . . . . .	31	„ „ . . . . .	43.9
Total . . . . .	63	„ „ . . . . .	<u>46.4</u>

The order of frequency of the various conditions was as follows—

Addison's anæmia . . . . .	6 cases
Subacute combined degeneration of cord (two with definite Addison's anæmia) . . . . .	5 „
Chronic gastritis . . . . .	5 „
Gastro-jejunostomy sequelæ . . . . .	4 „
Carcinoma of stomach . . . . .	3 „
Rheumatoid arthritis . . . . .	3 „

2. *Hypochlorhydria Group.*

Males . . . . .	24	Average age . . . . .	46.5
Females . . . . .	29	„ „ . . . . .	43.7
Total . . . . .	53	„ „ . . . . .	<u>45.0</u>

The order of frequency of the various conditions was as follows—

Neurasthenia . . . . .	6 cases
Visceroptosis (including gastropotosis) . . . . .	5 „
Gastro-jejunostomy sequelæ . . . . .	4 „
Nervous dyspepsia . . . . .	4 „
Carcinoma of Stomach . . . . .	3 „
Gastric ulcer . . . . .	3 „

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### 3. *Low Normal Group.*

Males	. 18	Average age	. . 39.1
Females	. 28	„ „	. . 41.7
	<hr/>		
Total	. 46	„ „	. . 40.7
			<hr/>

The order of frequency of the various conditions was as follows—

Visceroptosis (including gastroptosis)	. 5 cases
Gastro-jejunosotomy sequelæ	. . 5 „
Gastric ulcer	. . . . 4 „
Duodenal ulcer	. . . . 4 „
Nervous dyspepsia	. . . . 3 „

### 4. *Normal Group.*

Males	. 58	Average age	. . 42.0
Females	. 54	„ „	. . 35.8
	<hr/>		
Total	. 112	„ „	. . 39.0
			<hr/>

The order of frequency of the various conditions was as follows—

Nervous dyspepsia	. . . . 10 cases
Constipation	. . . . 7 „
Chronic appendicitis	. . . . 6 „
Gastric ulcer	. . . . 5 „
Neurasthenia	. . . . 5 „
Psychasthenia	. . . . 5 „
Gastro-jejunosotomy sequelæ	. . . . 4 „
Gallstones	. . . . 4 „
Chronic colitis	. . . . 4 „

### 5. *High Normal Group.*

Males	. 29	Average age	. . 42.9
Females	. 18	„ „	. . 34.8
	<hr/>		
Total	. 47	„ „	. . 39.7
			<hr/>

The order of frequency of the various conditions was as follows—

Duodenal ulcer	. . . . 9 cases
Gastric ulcer	. . . . 6 „
Nervous dyspepsia	. . . . 3 „
Chronic colitis	. . . . 3 „

### 6. *Hyperchlorhydria Group.*

Males	. 71	Average age	. . 47.0
Females	. 33	„ „	. . 43.9
	<hr/>		
Total	. 104	„ „	. . 46.0
			<hr/>

The order of frequency of the various conditions was as follows—

Duodenal ulcer . . . .	18 cases
Nervous dyspepsia . . . .	15 „
Gastric ulcer . . . .	5 „
Neurasthenia . . . .	5 „
Gastro-jejunostomy sequelæ . . . .	4 „
Visceroptosis (including gastropptosis)	4 „
Chronic appendicitis . . . .	3 „
Rheumatoid arthritis . . . .	3 „

#### *Rate of Emptying of Stomach in Achlorhydria*

The statement is frequently made, and it would appear to be the general belief, that when free hydrochloric acid is absent, the stomach empties much more rapidly than normal.

There are considerable variations in the time taken for even normal stomachs to empty, but Bennett and Ryle<sup>3</sup> found that the average time was 1·9 hours, using the standard meal of oatmeal gruel.

In the same way, achlorhydria cases may empty as early as 0·5 hours, but there may also be marked delay, even up to 3·25 hours, as observed in the present series.

It was not possible to ascertain exactly the relative importance of the several factors influencing the rate of emptying of the stomach in a sufficiently large number of cases. A fair comparison may, however, be made with the normal average time of 1·9 hours, and this has been done.

Of the 63 cases of achlorhydria, 51 were selected as being reliable for this purpose. Those excluded were not those showing rapid emptying, but consisted mainly of analyses where a note as to the time of emptying had been omitted.

The total time of emptying, as determined by the absence of a strong starch-iodine colour, was 82 hours, giving an average rate of 1·60 hours.

Specimens containing traces of starch were not considered as evidence of appreciable quantity of food remaining in the stomach, and were not included. The sugar-reaction was not noted in the majority of the analyses, and has not been accepted as an indication of the presence of food in the stomach.

Of these 51 cases, there were 19 in which the test had been terminated although starch was still present in the last specimen. It would be unfair to include 7 of these cases in which the test ended at 1½ hours or less, for there was no evidence that the stomach was empty at that stage. Further, the

inclusion of the remaining 12 analyses uncompleted at  $1\frac{3}{4}$  hours and upwards, fully compensates for the exclusion of the 7.

The total time of emptying of the 44 cases was 73·25 hours, giving an average time of 1·66 hours. In my opinion, this is the minimum average figure for the time of emptying of the stomach in this series of achlorhydria cases.

Thus, the average rate of emptying of the stomach in cases of achlorhydria is only a quarter of an hour less than the average normal rate.

The above conclusion is based upon the fractional method of gastric analysis alone, and it was, unfortunately, impossible to confirm the results by x-ray examination.

These figures, however, seem to suggest that rapid emptying of the stomach in cases of achlorhydria is not the rule.

In conclusion, I wish to thank Dr. A. F. Hurst for his advice whilst compiling these notes, and for permission to publish them.

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<sup>2</sup> A. O. Haneborg: *Acta Med. Scand.*, Supp. i. 117, 1921.

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## OBSTRUCTION OF THE URETER BY ABNORMAL RENAL BLOOD-VESSELS

By R. P. ROWLANDS, M.S., Surgeon to Guy's Hospital.

THE object of this communication is to draw attention to the importance of kinking of the ureter over an abnormal blood-vessel as a cause of renal colic, hydronephrosis and stone in the kidney. In 1894 Newton Pitt<sup>1</sup> drew special attention to "aberrant renal vessels as a cause of hydronephrosis" and showed before the Pathological Society five specimens taken from the post-mortem room. Three of these are in the Guy's Hospital Museum (Spec. 1693, 1694, 1695), and Sir Henry Morris<sup>2</sup> figures two of them in his classical work on *Surgical Diseases of the Kidney and Ureter*.

Commenting on these specimens, Newton Pitt said: "Though but few cases of hydronephrosis due to aberrant vessels have been recorded, it certainly is not very uncommon. This association is frequently overlooked, owing to the kidneys being removed singly from the body. Dr. Fagge refers to hydronephrosis due to a hypothetically misplaced vessel, but most authorities overlook it altogether. Sir William Roberts refers in his work on *Urinary and Renal Diseases* to two among fifty-two cases of hydronephrosis in which a supernumerary renal artery compressed the ureter near its origin. . . . As a practical point in operating upon cases of hydronephrosis without obvious cause, it would be worth while to examine the lower and posterior part of the pelvis, near the orifice of the ureter, for an aberrant vessel, and, if found, it might be ligatured and divided, probably with the best results."

In spite of these writings by old Guy's men, so few practitioners know of this condition that it is usually overlooked for years; the patient suffers from repeated attacks of severe pain, and ultimately the affected kidney becomes seriously damaged before relief is given by operation. Some of my patients had consulted a great many doctors and specialists before a correct diagnosis was made and a cure afforded by operation (see Cases 11 and 12).

Dietl in 1864 described these "crises" in connection with movable kidney, and attributed them to twisting or kinking of the renal vessels or ureter by the descent of the kidney. But Dietl's crises may occur without abnormal mobility of the

kidney, and they have nothing to do with obstruction of the renal vessels. They are due to obstruction of the ureter, causing intermittent hydronephrosis. Mobility of the kidney, primary or secondary to the hydronephrosis, may aggravate the symptoms, but apart from obstruction of the ureter, movable kidney is of little importance, although many symptoms are wrongly attributed to it.

I have met this condition twelve times in the last twelve years; I published eight examples in 1917.<sup>3</sup> Congenital stricture with valve formation at the junction of the ureter and pelvis of the kidney is another important cause of similar symptoms, which cannot be discussed fully here. *These abnormalities will be found to be not uncommon if the pelvis and the ureter are carefully examined as a routine and essential part of every kidney operation.* Nephropexy should never be performed until obstruction of the ureter has been definitely excluded as a cause of the symptoms. Many failures of nephropexy, like Case 6, are undoubtedly due to mistaken diagnosis. Similarly, nephrolithotomy is not likely to be permanently successful if the stone has been caused by an obstruction of the ureter, which is not discovered and relieved at the operation. In three cases illustrating this paper—Cases 3, 7 and 10—stones had formed behind the obstruction caused by an abnormal renal vessel.

The early recognition and treatment of this condition relieves the patient from frequent and disabling attacks of pain and saves the kidney from gradual destruction.

#### PATHOLOGY

The main renal vessels and their branches pass in front of the renal pelvis to reach the hilum of the kidney, but one of the four or five branches of the renal artery or vein usually passes behind the pelvis, as a rule at too high a level to obstruct the narrow outlet into the ureter. Occasionally, however, an abnormal renal vessel crosses the origin of the ureter on its way to the lower pole of the kidney. This is usually an abnormal posterior branch of the renal artery. Sometimes a similar tributary of the renal vein, and sometimes a vein and an artery, run together. Very rarely, an additional renal artery runs from the aorta to the lower end of the kidney. As a rule, but not invariably, the offending vessel lies behind and hitches up the origin of the ureter (Fig. 1). The abnormality appears to be about equally common in the two kidneys, and in males and females. In some cases the abnormal vessel crosses the ureter without obstructing it, but if the kidney is unusually movable some obstruction is likely to occur when the trunk is in the vertical position. This leads to gradual dilatation of the



pelvis. Any dilatation and pouching of the pelvis is likely to increase the tension upon the artery and therefore to increase the obstruction. In the course of time, as the pelvis becomes more and more distended and as the heavier kidney descends more, the tense blood-vessel exerts more and more pressure on the ureter, inflaming it, and at last causing a real stricture at the site of constriction (Cases 3 to 9).

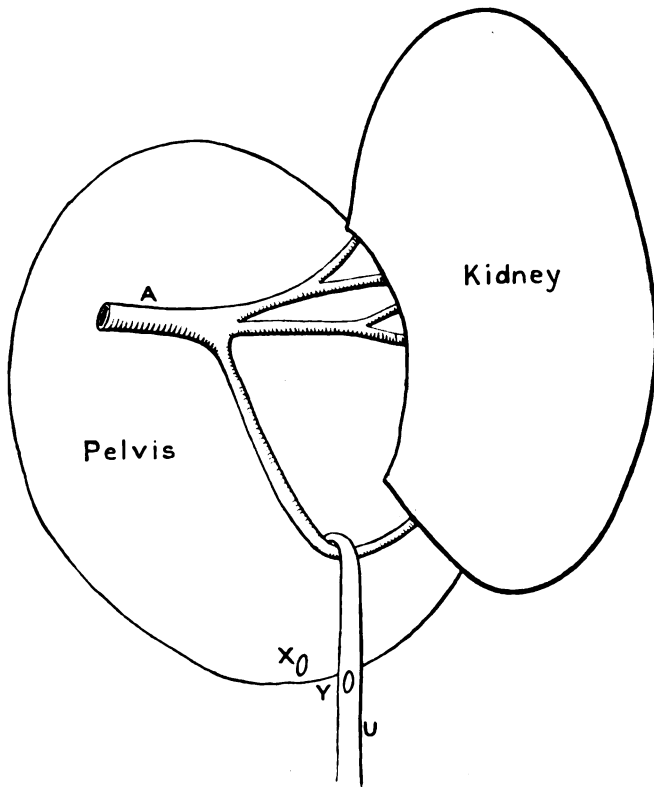


FIG. 1.

Diagram of obstruction of a ureter by an abnormal vessel. A, renal artery, a branch of which hitches up the ureter, U, at its origin. The division of the abnormal vessel is sufficient in mild cases, but a plastic operation or a short circuit at X and Y is necessary in severe cases.

#### SYMPTOMS AND SIGNS

1. Attacks of renal colic of increasing frequency and severity which may go on for years before the condition is recognised. As a rule, the patients are over twenty-five before an operation is considered, but the symptoms may begin in childhood (Cases 11 and 12).

Exercise is apt to bring on these attacks of sudden spasmodic, characteristic, and severe pain, which runs from the loin downwards and inwards into the groin, and often into the testicle,

which may be retracted. In some cases the pain runs down the front of the thigh; in a few it does not extend to the groin, but is a semi-girdle pain about the level of the umbilicus. As a rule the pain is intolerable, the patient cannot sleep or lie still; nausea and vomiting are often associated with it, and there may be faintness, pallor, or even shivering. Generally there is some abnormality of micturition, usually increased frequency and irritability with a diminished quantity of urine. At first the urine, during and after an attack, is normal in character; later it may be albuminous or even contain blood or pus. Occasionally the amount of urine passed is increased just after an attack. Usually there is deep tenderness and rigidity in the loin during an attack and sometimes in late cases a swelling can be felt descending below the costal margin on deep inspiration. Early attacks are often far less severe. Sometimes there is shivering and in late cases a rise of temperature.

2. In the interval between the attacks there is at times a dull ache, a sense of fullness, or a dragging pain in the loin.

3. In time the general health deteriorates and the kidney becomes chronically distended, palpable, and tender.

#### DIAGNOSIS

A. *Renal colic has to be distinguished from other severe pains in this region*, especially appendical, biliary, and intestinal colic. Appendical is rarely so severe as renal colic and is not often associated with urinary symptoms, except when the appendix is low down, near the bladder, or is lying close to the ureter. As a rule, there is tenderness over the appendix and more intestinal symptoms, such as chronic indigestion and, perhaps, a slight elevation of temperature, which is rare with renal colic. Intestinal colic, ~~due to lead~~, is characterised by the lead line, punctate basophilia and constipation, and is mostly located about the umbilicus; there is often generalised abdominal tenderness. In one of my patients the abdomen had been opened on the assumption that he had an ileal kink (Case 8). The spasmodic attacks of pain with tenderness in the loin sometimes caused by posterior duodenal ulcer have led to an erroneous diagnosis of renal colic with exploration of the loin. Biliary colic is higher in position and chiefly located in the right hypochondriac and epigastric regions. Tenderness is just below the ninth costal cartilages, except when the gall-bladder is unusually low.

B. *The various causes of renal colic have to be distinguished from each other.*—Attention therefore may be drawn to some of the most important causes of obstruction in the ureter.

1. *Foreign bodies inside the ureter.*—Stone or gravel; blood clot from injury, growth or tuberculous disease of the kidney; tuberculous débris blocking the narrow channel of a tuberculous ureter; small hydatid cysts passing down the ureter.

2. *Changes in ureteral wall.*—Stricture, congenital or acquired; valve formation at junction of pelvis and ureter; myoma or other growths of the ureter.

3. *Pressure upon the ureter* by abnormal blood-vessels, especially when the kidney is unduly movable; growth, especially of the uterus. I have known an abscess in the lower end of the only kidney completely and fatally obstruct the ureter.

Of all these stone gives the most severe pain; it is most frequently associated with bleeding and excess of crystals in the urine. Severe bleeding is quite rare with the other causes of renal colic, except tuberculosis and growth of the kidney. Severe bleeding, giving rise to colic, is only occasional with tubercle; the ureter is somewhat narrowed, and clots or débris cannot pass easily through the strictured tube. A similar stricture of the ureter is sometimes due to bilharzia.

An x-ray examination should always be made, *but a negative report as regards stone in the ureter is not conclusive for many reasons.* A stone obstructing the ureter is usually small, except when it is merely projecting into the ureter from the pelvis. The patients are often over middle age and somewhat stout. The stone may be composed of urates which cast but little shadow. I have operated on a number of cases and removed one or more stones from the ureter when the x-ray report was negative. In one instance the patient had been radiographed five times at different hospitals, and I removed a stone, the size of a filbert, from the upper part of his ureter. In these cases cystoscopy is of the greatest value. Two grains of indigo-carmin are injected into the thigh, and twenty minutes later coloured urine ought to be seen issuing from both ureters. The absence or marked diminution of the stream from one ureter is of the greatest significance, and the loin should be explored. In some cases a stone is seen projecting into the bladder from the lower end of the ureter. In others, it can be felt just above the bladder through the anterior wall of the vagina.

Pyelography is of value in the diagnosis of early hydronephrosis and may help in localising the cause. Diminution of urine during the pain, with increase afterwards, is suggestive of hydronephrosis. In a few of these cases some swelling can be felt on careful examination during an attack, and the kidney is tender on palpation. Cystoscopy with the aid of indigo-

carmine is also invaluable, especially during an attack. In some late cases the pelvis can be felt independently from and internal to the lower part of the kidney.

It is almost impossible to distinguish between an abnormal artery, a stricture or valve formation, and a small stone in the ureter as a cause of early hydronephrosis, and exploration is the only certain way of ascertaining the cause and treating the condition. Occasionally a movable kidney may give rise to pains, which are indistinguishable from those of obstruction of the ureter, and yet the pelvis when examined is found to be normal. Bacilluria is not a cause of renal pain, but is a common pitfall, for it is easy to be satisfied with the diagnosis of bacilluria, when there is a real mechanical cause of obstruction, which indirectly causes bacilluria. In the early and hopeful stages of hydronephrosis, however, the urine is sterile, and it may remain normal in every respect for years, but slight albuminuria sometimes accompanies or follows an attack of colic. Later secondary and destructive infections may occur. In the early stages the absence of pathological products in the urine misleads, for it is difficult to realise that any serious changes are going on in the kidney, and in many instances the attacks are thought to be neurotic, gastric, or even intestinal in origin.

#### TREATMENT

Our aim should be to recognise and treat this interesting condition before the kidney, pelvis, and ureter are seriously damaged. Secondary changes in the kidney unfortunately called for nephrectomy in Case 3, as it probably has done in many other cases of hydronephrosis and pyonephrosis due to an abnormal vessel which was not discovered at the operation. Moreover, the changes in the pelvis and ureter demanded a plastic operation to ensure efficient drainage in half of my cases. How much simpler it is when division of the abnormal vessel is sufficient. When severe and long-continued pressure has caused a stricture to form at the origin of the ureter or extreme dilatation of the pelvis with relative elevation and valvulation of the ureteral orifice, a plastic operation is imperative. At first I performed Fenger's operation (after Finney's method of gastroduodenostomy), but this is more difficult and not so satisfactory as making a short-circuit between the lower part of the pelvic pouch and the ureter at the same level or a little lower down. With a shorter incision this ensures a better drainage from the lowest part of the pool, especially when the hydronephrosis is of large size. If the opening in the pelvis is round and also a little larger than the one in the ureter, a more patent channel is established. Nephrectomy should be reserved for extreme

cases, where the renal cortex is thin or white or otherwise hopelessly damaged, for the regenerative powers of the kidney are wonderful under good conditions of drainage and asepsis. Excision of part of the dilated pelvis is rarely necessary, as, when well-drained, it contracts rapidly.

#### NOTES OF CASES

Eight of the following cases were published in full in the *British Medical Journal*.<sup>3</sup> These notes have been greatly abbreviated here to save space.

##### Case 1.—*Left Hydronephrosis*

A woman, aged 35. Recurrent obscure colicky pains in left flank and along the ureter. Urine normal. Radiography for stone negative. Cystoscopy with indigo-carmin indicated nearly complete obstruction of the left ureter. Exploration of left loin revealed hydronephrosis due to abnormal renal vessels passing behind the origin of the ureter to the lower pole of the kidney. These were divided and the obstruction relieved. The patient died four days later from perforation of a chronic solitary ulcer of the lower end of the ileum. Microscopic examination showed no definite evidence of tuberculosis.

##### Case 2.—*Left Hydronephrosis*

Miss H., aged 36. For five or six years patient had had attacks of pain in the left loin, shooting down towards the groin, sometimes very severe and only relieved by morphia. The urine was always normal. A kidney truss gave no relief. During the attack of pain a swelling appeared in the left loin, but usually disappeared when the patient lay down. At last a very severe attack occurred and a large swelling appeared in the left flank, which hardly moved upon respiration and had not since diminished. The urine was still normal. The swelling was mostly resonant in front and was thought to be the distended renal pelvis. An x-ray examination had failed to show any stone. Cystoscopy with the aid of indigo-carmin showed nothing issuing from the left ureter, but pigment came away from the right after eight minutes. At the end of twenty minutes nothing had come from the left. The kidney was found to be enormously enlarged and was, with some difficulty, shelled from its surroundings and delivered into the wound. It was then noticed that the obstruction to the ureter was due to the hooking of an artery extending into the lower pole of the kidney in front of the beginning of the ureter, the pelvis having descended in front of this abnormal vessel. The obstruction was complete. The ureter itself was natural. On ligaturing and dividing the vessel the junction of the ureter and pelvis was seen to be natural and not narrowed, although there were some adhesions. With a little difficulty 16 oz. of urine were squeezed from the kidney to the bladder without

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incising the kidney or pelvis. When the kidney had been quite emptied nephrorrhaphy was performed. The patient made a good recovery.

### Case 3.—*Right Hydronephrosis : Stone : Secondary Nephrectomy*

Mrs. B., aged 30, had had attacks of pain in the right flank without pyrexia. The appendix was removed without relief. Six months later the kidney was explored and the renal pelvis was found moderately dilated owing to an abnormal renal artery, which passed behind the junction of the ureter and pelvis and constricted the channel; when the kidney descended a considerable pouch came down behind the abnormal artery. On dividing the artery a marked constriction was still present at the junction of the ureter and pelvis, and the opening of the ureter was about two inches above the lower pole of the pelvis. The opening was enlarged after Fenger's method, and the kidney was examined through the opening. No stone, but a collection of grit in an abscess the size of a filbert was found at the lower end of the kidney. This was scraped away and the cavity drained. As the kidney was somewhat movable nephropexy was performed.

About a year later the patient began to have attacks of renal colic again, and the x-rays showed a stone in the right kidney, which was removed in 1915. After this she had occasional, slight attacks of colic, and I had her x-rayed once or twice with negative results. On February 15, 1917, she came to hospital, suffering very severely from renal colic and looking very ill. She had rigors and a temperature of 103°. This continued the next day, and the loin, which was at first very full, became slacker, and the urine, which was at first clear, became blood-stained. I explored the right loin and found the kidney to be shrivelled and whitish from chronic nephritis, and also loose within its capsule with some fluid in the latter. The pelvis was still dilated and contained a very large number of smooth, dark pieces of altered blood of various shapes and sizes. There was no stone. The kidney was so disorganised that I thought it wise to remove it. The patient recovered, but had albuminuria some four years later.

### Case 4.—*Left Hydronephrosis*

A man, aged 45, had had repeated attacks of typical renal colic in the left side during the last eighteen months. He was skiagraphed several times with a negative result. The urine was normal on repeated examinations. The lower pole of the left kidney could be felt. A belt was tried without relief. The attacks became more and more frequent and severe, and at one time laid the patient up for three months. He at last begged for operation. He never had any hæmaturia nor variation in the amount of urine passed. The kidney was explored and a dilated pelvis found. An abnormal renal vessel was seen, the condition being very similar to that described in

Case 3; the same treatment was adopted. A catheter was passed from the pelvis of the kidney through the sutured part and down the ureter for three days. The patient had a good deal of extravasation of urine along the course of the ureter, and pain and distension of the abdomen for a few days, but he made a good recovery.

It is far better not to leave a catheter in the ureter, but to aim for a free passage with a water-tight junction. The convalescence is thereby made safer, easier, and shorter.

#### Case 5.—*Right Hydronephrosis*

A man, aged 50, had had several attacks of right renal colic. X-ray examination for stone negative. Definite swelling in the right loin, when the patient came to the Out Patients' Department.

The kidney was exposed and a moderate degree of hydronephrosis was found, due to an abnormal artery and vein, apparently running from the renal vessels downwards and outwards to the lower pole of the kidney and passing in front of the ureter at its origin, hitching it up and completely obstructing it. The vessels were tied and divided; some of the urine could then, with some difficulty, be squeezed out of the pelvis into the ureter. This made it apparent that there was a stricture of the ureter at the site of constriction, probably due to secondary inflammation. A plastic operation was performed after Fenger's method, a large opening, one inch long, being made. The patient made a good recovery.

#### Case 6.—*Right Pyonephrosis: Abnormal Vessel: Nephropexy had failed*

A soldier, aged 25, had had several attacks of colic in his right side before the war. He had more while in Malta, where he was seen by several surgeons and was examined with the x-rays; they ultimately came to the conclusion that his attacks of violent colic were due to a movable kidney. Nephropexy was performed, but the patient had two attacks after the operation. He says that he had no pus in the urine before the operation, but in the two attacks he had had since then—one in Malta and one after coming home to England—pyuria was present. He had a third attack, and was admitted into the 2nd London General Hospital, where I saw him, and felt a large, tender right kidney. There was no pus in the urine. The temperature kept up for two or three days; an enema was then given and was followed by sudden relief, with the passage of large quantities of pus in the urine. Apparently the enema relieved a kinked ureter. He was then better for a week, but still had pyuria. A pure cultivation of *B. coli* was obtained from the urine. He had another attack, again relieved by an enema, and was then anxious to have an operation done. The diagnosis was "a kinked ureter possibly due to an abnormal vessel, or possibly obstruction due to a small calculus." Repeated x-ray examinations, however, had not revealed any calculus.

I found the scar of rather a small incision high up, close to the last rib. I made a much longer one below the original and found the old stitches. The kidney was tethered by them still, but was considerably enlarged and very vascular. It was difficult to mobilise without decapsulation, which I had to do, and I then found it could not be delivered owing to adhesions around the pelvis. The ureter was normal in size and was followed up through a constriction in the surrounding tissues to a distended pelvis. The posterior part of the ring was divided and found to be of fibrous tissue. The anterior part was formed by two large blood-vessels, and they clearly constituted the main obstruction and corresponded to the junction of the pelvis and ureter. The two vessels were tied and divided. They entered the lower pole of the kidney and apparently came from the main renal vessels. Owing to the length of the ureter, size of the pelvis, and the adhesions around them, the division of the vessels did not entirely obliterate the kink. As the kidney was returned into its bed the kink became more marked. I therefore tried to straighten out the ureter by sewing it to the lower part of the kidney, but, as this did not seem satisfactory, I performed an anastomosis after Fenger's method and the result was good. A large quantity of pus was evacuated and it was interesting to see it find its way down into the ureter directly the constriction formed by the blood-vessels was divided and the ureter straightened out. The kidney was considerably inflamed and had white spots in the cortex, probably indicating small foci of suppuration. The patient made an uninterrupted recovery, the wound healing primarily in spite of the pus evacuated at the operation.

Case 7.—*Abnormal Artery causing Obstructed Ureter ; Stone in Left Kidney*

G. L., a boy, aged 12, for two years had hæmaturia and pain at intervals in the left loin and flank. X-ray examination revealed a stone in the pelvis of the left kidney. The kidney was difficult to bring out of the wound owing to an abnormal artery entering the lower pole. It clearly constricted the ureter just below the pelvis and was therefore divided. The pelvis was dilated and inflamed. I incised it and removed an isolated calculus the size of a filbert. The patient made a good recovery.

Case 8.—*Left Hydronephrosis : Abnormal Renal Artery : Previous Operation for Supposed Ileal Kink*

Lieut. H., aged 28, had had repeated attacks of colic in the left flank for the last ten years. Eighteen months before x-ray examinations had revealed no stone and no renal tenderness. An operation was not advised and he went to a Convalescent Home. The doctor there thought he had an ileal kink and sent him to another surgeon who operated. He made a very long incision in the abdomen, found the appendix normal, and said that he released an ileal kink. The attacks continued.



The patient was sent to Sussex Lodge again for observation, and one day, when I happened to be there, the pain came on. The left kidney was palpable and was very tender both in front and behind. I advised operation, having diagnosed an obstructed ureter, possibly due to an abnormal artery, a small calculus or a valve.

A large hydronephrosis, the pelvis being the size of an orange, was caused by an abnormal renal vein, passing from the main renal vein downwards behind the ureter at its origin and then forwards to the lower pole of the kidney. On dividing this it was noticed that the ureter was narrowed at its origin. To make sure of effecting a cure, an anastomosis was made between the back of the pelvis and the ureter an inch down. A catheter had previously been passed along the ureter into the bladder without any difficulty, and a finger had been introduced into the pelvis and calices without finding any stone. The exploratory opening in the back of the pelvis was used for the anastomosis. It was noticed that the ureter in its upper two inches was inflamed and dilated, and it appeared probable that under certain conditions the artery constricted the ureter below this dilated part, but that it slipped up as the pelvis became more distended. The patient made a good and rapid recovery.

#### Case 9.—*Left Hydronephrosis : Abnormal Vessels*

Mrs. E. W., aged 49, had a history of violent pain and swelling in the left loin for eighteen years. Seventeen years ago she was "tapped," and a nephropexy was performed.

She had relief for ten years, but since then has had increasing attacks of pain and swelling in the left flank. X-ray examination for stone negative. There were oxalate crystals in the urine, a few pus cells, slight albuminuria and *B. coli* on cultivation. Urea in the blood three times the normal. A diagnosis of obstruction of the ureter by abnormal vessel or valve ureter was made.

The ureter was found to be constricted by an abnormal artery and vein, passing behind it and kinking it at its junction with the pelvis. These vessels were divided, but a constriction remained and a valve was present at the junction of the ureter and pelvis. The opening was enlarged after Fenger's method. The abnormal vessel came as usual from the renal vessels. The patient made a good recovery.

#### Case 10.—*Left Hydronephrosis : Calculus*

Boy, aged 12, had symptoms and showed an x-ray shadow of stone in the kidney.

A large oxalate stone was found in the left kidney near the lower calyx, and an abnormal renal artery passed from the main renal artery to the lower pole of the kidney behind the junction of the pelvis and ureter, kinking the latter. The artery was divided and the stone removed through the cortex. The pelvis was dilated. The patient recovered rapidly.

Case 11.—*Right Hydronephrosis*

Mr. A. M., aged 18½, described his illness as having started at the age of eight or nine years, severe attacks of pain occurring every two to three weeks. During the next ten years many x-ray examinations were made with negative results, and many doctors consulted, but no definite conclusion was arrived at as to the cause of the symptoms. The attacks now increased in severity and lasted from five to seven days, morphia having to be given for the relief of pain. The urine was normal. At the beginning of 1920 a urologist, after pyelography, diagnosed hydronephrosis and advised immediate removal of the right kidney, but a physician, who suspected a stricture or kink of the ureter, brought the patient to see me. I diagnosed hydronephrosis due to an aberrant renal vessel or valvulation of the origin of the ureter. The patient's father then took him abroad to consult various continental experts. Dr. — of Brussels diagnosed auto-intoxication and strongly recommended medical treatment, while Professor I. of Berlin, after very thorough examinations, recommended nephrectomy as an imperative necessity. The patient returned to London and saw several more consultants. In all he had consulted about twenty medical men before he asked me to operate.

On September 28, 1920, I found that no urine issued from the right ureter. An abnormal vein was discovered behind it, kinking it just below the renal pelvis, which was moderately dilated. The kidney was in good condition. The vein was divided and the patient made a good recovery. He has remained well and has led a very active life since the operation.

Case 12.—*Right Hydronephrosis*

Miss M., aged 21, had for six years suffered from abdominal pain and pain in the right lumbar region at irregular intervals. Of recent years it had been more severe in character and lasted longer. It was more or less continuous, with fairly frequent severe paroxysms. During the latter the patient turned very pale, sweated, and sometimes fainted. During the attacks she was continuously and violently sick; she was constipated and could not pass any urine at all until the first paroxysm was over, and then she passed a large quantity. The urine contained a slight trace of albumin, a trace of blood, some calcium oxalate crystals, blood corpuscles, and squamous cells. During the attacks there was no fever, but the pulse rate ran up to 120. The pain seemed to extend over the whole of the right abdomen, the right hypochondriac region, back and front, and was especially severe down the course of the ilio-inguinal and ilio-hypogastric nerves. The abdominal muscles were held tense so that nothing could be made out during an attack, which usually lasted three or four days and left the patient sore. X-ray examinations on two occasions failed to reveal the presence of a stone.

I was the thirty-seventh medical man the patient had consulted. I diagnosed hydronephrosis due to aberrant renal vessel or valve ureter.

Cystoscopic examination on February 2, 1922, showed no urine issuing from the right ureter. The right kidney was explored at once. It was large and hydronephrotic owing to an abnormal renal artery and vein arising in the renal vessel running behind the ureter to the lower pole of the kidney. This was divided and the kidney fixed. There was no stone. The patient improved greatly, but subsequently had another attack of pain and passed some organised clot, which had probably blocked the ureter. Since then she has done well.

#### CONCLUSIONS

A careful study of these cases leads to several important conclusions.

(1) The long duration of unnecessary suffering, the large number of medical men consulted before the correct diagnosis is made and the only rational treatment by operation is adopted shows that we are not sufficiently aware of the possibility and curability of this interesting condition.

(2) Cystoscopy after the injection of indigo-carmin is very valuable in establishing the diagnosis and in ascertaining the functional capacity of the other kidney.

(3) It is very important at all operations upon the kidney and upper ureter to look out for abnormal vessels kinking the ureter, so that a complete cure can be made at one operation.

(4) The difficulties of secondary operations owing to adhesions and secondary changes in the kidney and ureter point to the value of finding and dividing the abnormal vessel at the first operation. In six out of twelve of my cases a secondary stricture of the ureter, due to long-continued pressure of the obstructing blood-vessel, had to be overcome by a plastic operation, and in one a secondary nephrectomy became necessary. Earlier diagnosis and more thorough operations should make these complications very rare.

(5) Once the obstruction is thoroughly overcome the recoverability of the kidney is very remarkable. Primary nephrectomy—even if the other kidney is known to be good—should therefore be very rarely performed. It is far wiser to give the damaged kidney a chance of recovery unless it is in a hopeless and dangerous condition.

(6) When a secondary stricture of the ureter has developed, a plastic operation or anastomosis with a water-tight junction will probably save the kidney, even in the presence of pyonephrosis (Case 6).

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## SPASTIC RETRACTION OF THE TESTICLE

By PHILIP TURNER, M.S., Surgeon to Guy's Hospital.

THE condition, to which the above name may be given, is one of considerable importance, since it may very easily be confused with true imperfect descent of the testicle. The necessity for recognising spastic retraction as a distinct condition is that operative treatment is not required; in true cases of imperfect descent of the testicle, except possibly in the first few years of life, operative measures are necessary in order to get the retained organ to the scrotum owing to certain definite anatomical arrangements which can be readily recognised and demonstrated. It is surprising how often patients are seen as out-patients, or even admitted direct to the wards for operation for imperfectly descended testicle, which on examination prove to be cases of spastic retraction in which operation is not required.

The essential difference between the two is that in spasmodic retraction the position of the testicle depends upon spasm, intermittent or continuous, of the cremaster muscle, whereas true imperfect descent of the testicle depends upon a failure of the normal developmental process, which brings about the migration of the testicle from the upper part of the peritoneal cavity to the scrotum.

The testicle is normally suspended from the abdominal wall by a sheath composed of infundibuliform, cremasteric, and intercolumnar fasciæ, which have definite attachments above, surround the spermatic cord, and spread out round the tunica vaginalis below. The action of the cremaster is well seen in the cremasteric reflex, which is especially well-marked in children. Here often the slightest touch on the inner side of the thigh will cause the testicle to be at once drawn up into the inguinal canal, where it may be impossible to feel it and where it may stay for some time. In some cases exposure of the patient alone will be sufficient to call the muscle into action. Spastic retraction is a still further increase in the excitability of this muscle.

In this condition the testicle may be nearly always situated in the inguinal region, and certainly any attempt at examination

will cause it to occupy this position. The condition may be first noticed by the parents, or it may be met with in the course of some routine medical examination. It may very closely resemble true bilateral imperfect descent of the testicle, especially when found at the first examination of the patient.

The clinical characters of spastic retraction are as follows—

1. It is, in typical cases, where the difficulty in diagnosis arises, always bilateral. It is true that in the course of an examination for a supposed hernia the cremaster may draw the testicle up, but it is generally obvious at once that this is nothing more than the ordinary cremasteric reflex, possibly rather exaggerated.

2. The history is usually unreliable: the patient will be too young, and the mother will often be unaware of the abnormality. If, however, there is a definite history that the testicles have at some time been seen in the normal situation, it is probably a case of cremasteric spasm.

3. The degree of development of the scrotum should be noted. In a case of true developmental imperfect descent the scrotum is often, but not always, imperfectly developed and may be quite rudimentary. In cases of cremasteric spasm, where the testicle occasionally occupies the normal position, the scrotum may be normal. Too much stress must not, however, be placed on this, as the size of the scrotum in young boys varies considerably.

4. When a case is examined, gentle but continued manipulation should be tried to coax the testicle from the inguinal canal down into the scrotum. If both testicles can be manipulated into the scrotum and held there without undue tension and without causing the patient pain, it is safe to regard the case as one of spastic retraction, which will in time get well without operation. In true developmental imperfect descent the testicle may often be made to emerge from the external abdominal ring, but it cannot be made to enter the scrotum; very commonly it turns upwards and outwards over Poupart's ligament towards the anterior superior spine. If any doubt exists in the surgeon's mind, these manipulations should be repeated.

5. In a typical case of spastic retraction there will be no hernia found on examination and no history of hernia. Any swelling noticed will prove to be the testicle itself. In either unilateral or bilateral cases, in which the testicle is obscured by the presence of a hernia, the question scarcely arises, as it will be very generally admitted that the hernia should be treated by operation and the position of the testicle will be cleared up at the operation.

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In true developmental imperfect descent manipulation will not be successful in getting the testicle into the scrotum on account of the following definite anatomical arrangements which can be readily recognised at an operation.

1. Its peritoneal connections. In a considerable proportion of cases there is an obvious hernia, and in the majority of those in which there is no obvious hernial swelling a "potential hernia," or patent funicular process, is found at the operation. Indeed the presence of a hernia or the probability of a potential hernia, is one of the great reasons for operating. It is true that every now and then one operates on a case, in which no patent funicular process is found, but here I prefer to say that one is not found rather than that it is definitely absent. The funicular process may be so narrow and so thin-walled that it is possible in some cases it may be overlooked. I cannot say definitely in what proportion of cases no funicular process is found, but it is very unusual and I should estimate it at about 5 per cent. The importance of the funicular process can be shown at an operation by attempting to pull the testicle down, when the process becomes tense and prevents it from reaching the scrotum.

2. There is a shortness of the sheath surrounding the spermatic cord and tunica vaginalis.

3. Even when the above structures have been dealt with, the attachment of the gubernaculum will prevent the testicle entering the scrotum.

In addition to the above, which always have to be dealt with, there are the two following possibilities, which are fortunately both unusual, as they probably will prevent a satisfactory result to the operation.

4. Shortness of the spermatic veins.

5. Shortness of the vas deferens. This is more likely to occur in young adults than in children.

In spastic retraction the above anatomical conditions are not present, and hence operative treatment is not necessary. In true developmental imperfect descent operation is necessary for the transference of the testicle to the scrotum, unless it is possible for other means to overcome them, and it is difficult to see what other method could possibly alter the peritoneal relations or obliterate a hernial sac in a child between the ages of six and twelve years.

The action, or rather over-action, of the cremaster is shown in a different way in certain rare cases in which an apparently normal and normally placed testicle has, as the result of some sudden strain or exertion, been drawn up into the inguinal

canal, where it has remained permanently, becoming clinically a case of imperfect descent. Jacobson, in his book *Diseases of the Male Organs of Generation*, mentions several such cases (p. 41). The explanation of these depends, I believe, upon the fact that, though apparently normal before the injury, a peritoneal arrangement, similar to that found in a true case of imperfect descent, is really present; that is, there is a potential hernia, with a patent funicular process, and that a mesorchium is present. I was rather sceptical as to the existence of this condition until about three years ago, when I had the following case admitted into Luke ward.

D. W., aged nineteen years, was admitted into Guy's Hospital in June 1919 with the following history. In June 1918, while engaged in his work as a sawyer, he strained himself severely while lifting the trunk of a tree weighing about eight hundredweight; he felt something slip up into his groin, and, on examining himself, found that the left testicle had disappeared from the scrotum. At the same time, or shortly after, a swelling appeared in the left groin. The patient, who was a well-developed sensible lad, stated that until this time both testicles had been present in the scrotum, and that they were of equal size; also that he had never suffered from hernia, and had never had any swelling in the groin. I personally interviewed his father and his mother, and they were emphatic that during childhood and infancy both testicles had been present in the scrotum and that no hernia or other inguinal swelling had ever been noticed. The retracted testicle had never since the accident returned to its normal position. On admission, there was a small but definite hernia, and the testicle, which could be felt in the inguinal canal, could be manipulated just through the external ring, but could not be made to enter the scrotum. The left side of the scrotum was normally developed and the right testicle was normal in size and position. At the operation the anatomical condition found was exactly that of a typically imperfectly descended testis; there was a large tunica vaginalis which was connected with the peritoneal cavity by means of a patent processus vaginalis, and the testicle was rather smaller than the normally placed right testicle.

The hernial sac was removed, and the left testicle was transplanted to the right side of the scrotum. The patient was seen again in March 1920. The testicle was then suspended normally and freely in the scrotum, but was at a slightly higher level than the right testicle. There had been no pain and there was no recurrence of the hernia.

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Here the same strain which drew the testicle up into the inguinal canal appears to have forced some abdominal viscus into the potential hernial sac for the first time. The pain produced was slight, and on admission to the hospital the sensation in the displaced testicle was diminished.

This and similar cases which have been recorded are of interest as showing the effect of sudden violent action of the cremaster. The fact that the testicle did not return to its original position may be explained by the presence of the hernia, as it is generally recognised that the presence of a hernia may interfere with the testicle entering the scrotum, in the same way that the presence of an imperfectly descended testicle in the inguinal canal may determine the development of an unusual form of hernia such as an interstitial hernia.

I think that a consideration of these cases will throw some light on the cases of spastic retraction of the testicle which occur in children.



## STUDIES ON TUMOUR FORMATION

By G. W. NICHOLSON, M.D., Lecturer in Morbid Histology, Guy's Hospital.

### III. TISSUE MALFORMATIONS. ANOMALIES OF POSITION AND OF BLENDING

1. *Pigmented Nævi, or Cutaneous Moles.*—Unna <sup>26</sup> in 1896 said about the nævus-cells that, granted their epithelial origin, they support Cohnheim's theory of displaced, dormant tumour-germs more simply and beautifully than any other fact. Their origin from the epidermis is now universally accepted, although opinions still differ as to their ultimate fate.

Moles, as they are commonly called, are probably always congenital; at any rate, they are often discovered at birth, or soon after. They possess a definite life history. A period of active growth or adolescence is followed by one of adult life, in which changes are slight or absent, and finally by one of regression and old age. Only in the first period can their mode of origin be studied. It is therefore necessary to examine them in children, while they are still flat, and before the papillomatous changes and the pedunculation to which they are liable in their later stages have supervened.

A young mole is covered by epidermis, with highly irregular, elongated and branched papillæ. The columnar basal cells, and to a lesser extent all those of the rete Malpighii are often deeply pigmented, especially in the deep parts of the papillæ. The hair-follicles, sebaceous and sweat-glands, if present, participate in the changes. The basal cells have a marked tendency to become loosened and to pass into the corium, becoming detached from the epidermis. This is usually most clearly apparent at the apices of the papillæ. But this loss of cohesion occurs within the substance of the papillæ as well; nests of oval or round cells with relatively small, darkly stained nuclei and homogeneous "glassy" cytoplasm resulting. These are the nævus-cells. They are generally more or less deeply pigmented. They lie loosely side by side, and are no longer organically connected with each other by prickles. These, as well as the protoplasmic fibrils, have undergone liquefaction and disappeared. The nests of nævus-cells are at first entirely intra-epithelial. Sooner or later, however, their epithelial covering gives way on the deep aspect of the papilla, and they are then partly surrounded by

connective tissue (Fig. 21). Fresh nests are constantly produced, and the old ones pass more and more deeply into the corium. They become entangled with other groups of nævus-cells, with the cells that have been split off from the apices of the papillæ and have undergone a similar transformation, and with the fixed and wandering cells of the connective tissue. They enter the tissue spaces of the corium and form irregular columns, which have usually lost their connections with the epidermis (Fig. 22).

Many of these loosened epidermal cells do not assume the characteristic form described, but are oval, flat, or branched. Multi-nucleated giant-cells are not uncommon. Depigmentation constantly takes place, the pigment being taken up and removed

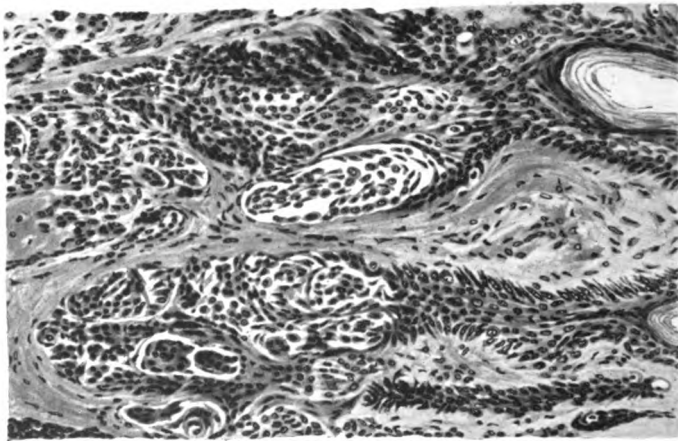


FIG. 21.

Pigmented mole. Extrusion of nævus-cells. Magnif., 175.

by leucocytes and the fixed cells of the corium, so that old quiescent moles often contain little or no pigment, except generally in the basal cells of their epithelial papillæ.

Moles often persist in this state for long periods of time. Sooner or later, however, the nævus-cells disappear and the corium between the epidermal papillæ then consists of a dense connective tissue, indicated in the upper right-hand corner of Fig. 22.

It is seen from the above description that the nævus-cells are of epithelial origin. They are, in fact, epidermal cells that have lost their fibrillation and prickles, and are therefore no longer in organic contact with each other. In other words, they have lost an essential epithelial character. They are cast out from the epidermis, and occupy the tissue spaces of the cutis.

It is necessary to inquire into the evidence as to where in the body pigment is produced. Wieting and Hamdi <sup>27</sup> have investigated this point. After a careful revision of the literature, and as the result of their own embryological and morphological studies, they come to the conclusion that pigment is only formed by epithelial cells. All the cells of the rete Malpighii can elaborate pigment, but certain cells, which are at first indistinguishable from the others of the basal layer among which they lie, become specialised in this direction. They are the melanoblasts (the chromatophores of writers), and are elongated, deeply pigmented cells, with long branched pseudopodia. Pigment that is produced in excess is carried into the cutis by the lymph. It is here

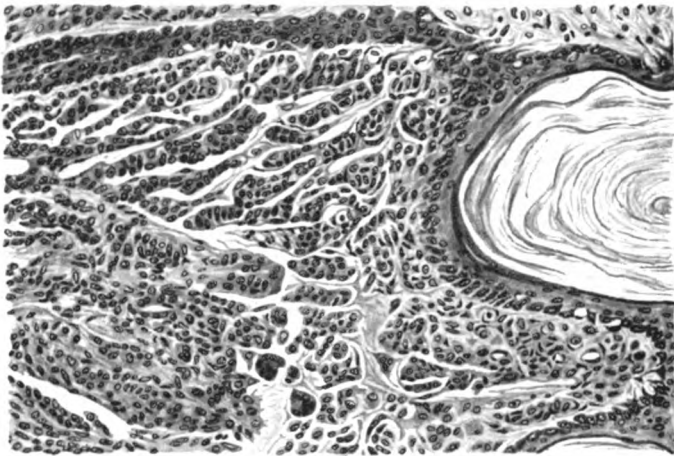


FIG. 22.

Pigmented mole. Nests of nævus-cells in cutis. Magnif., 175.

taken up by leucocytes and by connective tissue cells, many of which are branched. To the latter they limit the name of chromatophore. These cells store the pigment in the cutis, or carry it away to the lymph-glands, but never produce it. The epithelial origin of melanin is proved by its presence in the cells of the epidermis long before traces of it are found in the corium.

Although Wieting and Hamdi were unable to accomplish the impossible task of showing that the cells of the mesenchyme never participate in the elaboration of pigment, their arguments have rendered the assumption that it has a dual origin highly improbable. At any rate, they have definitely refuted Ribbert's <sup>22</sup> view that the chromatophores of the corium are the primary producers of pigment, and that they enter the epidermis and transfer it to its cells, a view which, on purely *a priori* grounds, is a very unlikely one. Ribbert's argument that the nævus-

cells are mesenchyme thus falls to the ground. He believed them to be undifferentiated chromatophores.

What is the status of the *nævus*-cells? Are they undifferentiated or degenerate? The evidence points very clearly to the latter view. Many writers, of whom Dalla Favera<sup>4</sup> is perhaps the most emphatic, maintain that they are degenerated cells, produced by liquefaction of the intracellular fibrils and prickles of the rete Malpighii, together with swelling and pyknotic nuclear changes, as a result of an excessive secretion of pigment. Before this pigmentary degeneration had set in, these cells possessed the same morphological characters as their neighbours. They therefore show no signs of having remained in an undifferentiated condition.

It remains for us to inquire into the fate of these cells. Opinions differ about it. The orthodox view is that they remain idle in the cutis for a considerable time, and are ultimately destroyed and replaced by a dense, often hyaline, connective tissue. The other view is the one put forward by Kromayer,<sup>12</sup> and defended by him in a long series of articles, as well as by a good many other writers. Kromayer upholds the view that in every part of the skin isolated epidermal cells constantly but slowly pass into the cutis, to reinforce its constituents. To this phenomenon he has given the name of *desmoplasia*.<sup>13</sup> In *nævi* many cells are rapidly and simultaneously extruded, without, however, necessarily becoming converted into connective tissue corpuscles (*para-desmoplasia*). Judalewitsch<sup>10</sup> asserts that the *nævus*-cells actually secrete connective tissue and elastic fibrils, and become true mesenchyme cells.

This view is unorthodox, but not inherently impossible or even improbable. It merely claims a repetition of the changes that take place in normal development during the formation of the mesenchyme. Our chief difficulty in accepting it is our respect for authority. I can see no reason why a process that occurs on a large scale in the embryo should not be repeated during the subsequent life of the individual. Every stage of development is, in great part, at least, a reaction to environment, a response to the conditions that affect the tissues. Why should not conditions occasionally arise in later life, conditions we are pleased to regard as abnormal, that are able to provoke a similar response? The only bar that I can see to this reaction is the complete exhaustion of the power so to react. But the long period of development over which the extrusion of the mesenchyme takes place, and its generalised distribution all over the body, render such an exhaustion improbable. Post-natal mesenchyme formation affords a rational explanation of

several kinds of tumours, as we shall have ample opportunities to see. The nævus-cells appear to me to be an excellent example of a belated attempt at mesenchyme formation, since the process by which they are cast off is essentially the same as that which occurs during the development of the mesenchyme of the embryo.

If we believe that the nævus-cells are converted into connective tissue corpuscles, the slow ageing and fibrosis that always take place in moles are readily explained. If we are not prepared to accept this view, there are no grounds for the belief that they lie dormant for indefinite periods of time. Even young moles show evidence of fibrosis and destruction of nævus-cells. Adult moles always show signs of the passage of isolated epidermal cells into the cutis, as well as of fibrosis of the latter (Fig. 22). In old hyaline moles the nævus-cells disappear, and the fibrosis dominates the picture. I conclude, therefore, that the nævus-cells have a definite life-history. They are extruded from the epidermis, rapidly at first, then more and more slowly. They are gradually either converted into connective tissue or destroyed. These two processes, or, to be accurate, the one we are prepared to accept, become more and more extensive as the age of the mole advances, a time being reached at which the elimination exceeds the production of nævus-cells.

There is, therefore, no evidence that nævus-cells are undifferentiated cells, since it points to the conclusion that they are degenerate. Nor is there evidence that these cells persist indefinitely in a functionless condition.

Cutaneous moles are probably always congenital anomalies, although occasionally they have first been noted in later life (*Nævi tardi*). Whether or not the latter have been present since before birth in a rudimentary state it is impossible to decide, since we have no knowledge of the histological appearances of the skin before their inception. I have, I believe, brought forward some evidence that the nævus-cells are not congenital, but that they are produced during the greater part of the life of the mole. I do not know the nature of the anomaly on the basis of which they arise. It appears to be a derangement of the regulation of pigment production. Its causation is quite obscure.

I wish to draw attention to Bettmann's<sup>2</sup> chapter on malformations of the skin. It is a fine attempt to explain them by means of external causes in preference to primary vices of the cells. He brings out most clearly the lamentable state of our ignorance of ante-natal pathology and of the mechanism of development.

According to the classification of tissue malformations I

have adopted, pigmented moles are anomalies of position morphologically, since they are characterised by the dislocation of epidermal cells, the *nævus*-cells, into the cutis.

2. *Accessory Suprarenals*.—No congenital displacement is probably better known than the pieces of suprarenal cortex that are found in a variety of situations. They have often been quoted as proof positive of the truth of Cohnheim's theory of tumour formation. Whether rightly or wrongly, I hope to show on a future occasion.

I do not at present propose to discuss the minute hyperplasias of the suprarenal cortex, except to point out that they merge by imperceptible degrees with the so-called adenomata. They illustrate the difficulty, or rather the impossibility, of deciding where hyperplasias end and tumour formation begins, and the truth of the contention in the first of these studies, that there are no essential differences between tumours and the normal tissues.

Nor are there appreciable differences between the cortical adenomata and certain accessory suprarenals, wherever situated. The latter are linear strips or round or oval nodules. When small, no demarcation into zones can be made out in these forms. In larger specimens, however, there is present a superficial *zona glomerulosa* beneath the whole of the circumference. It passes internally into a *zona fasciculata*. A *zona reticularis* is found at the centre; it may be solid, or contain one or more wide, thin-walled blood-vessels, surrounded by a varying amount of connective tissue. The epithelium presents all the characters of that of the suprarenal cortex. Vacuolation due to the presence of lipoids is often a marked feature, and gives the nodules their characteristic pale yellow colour. Minute areas of hyperplasia are not uncommon. A fibrous capsule partially or completely surrounds the accessory organ.

Were I to describe the adenomata of the cortex of the suprarenal, I should have to use identical words. They are indistinguishable from the accessory nodules.

The presence of zones in some accessory suprarenals, and their absence in others, does not necessarily mean that displacement has occurred at a late stage of development in the one case, after differentiation of the zones, or at an early period in the other. Nor does it imply that cells of all the layers were displaced together, or only those of one zone. There is no reason to suppose that all the cells of the cortex are not equivalent, and that they cannot replace and regenerate each other. Their morphological differences are due chiefly to their manner of grouping, and are caused by their position in relation to the

surface. The cells of the small accessory nodules would seem to be subjected to an environment which is too uniform to enable such differences to be produced. Traces of a superficial zona glomerulosa can, however, often be made out in very small specimens.

Within the substance of the suprarenal glands stages intermediate between the hyperplasias and the cortical adenomata, as they are generally named, can be made out. The latter sometimes attain a diameter of one or more centimetres. They are often surrounded by a capsule, but this may be absent, even in large specimens. They project above the surface or into the medulla of the gland, and are sometimes completely dislocated into, and surrounded by the cells of the latter. When they are

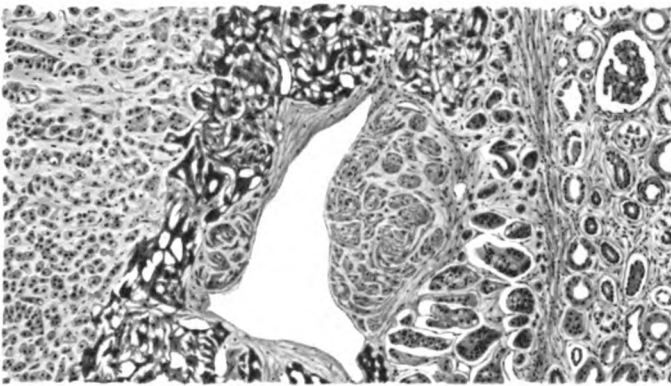


FIG. 23.

Accessory suprarenal on kidney. Cortex and medulla. Magnif., 90.

raised above the surface, they are covered superficially by the capsule of the gland. Others are pedunculated and attached by a bridge of cortex of varying thickness. Others, again, are united to the surface of the suprarenal only by their capsule. Yet others are free within the areolar tissue surrounding the gland. All the stages of dislocation and emigration, and of the production of accessory nodules, are thus represented by them.

I have seen an oval encapsulated accessory suprarenal among the ganglia of the solar plexus. It measures 5 mm. in its greatest diameter, and is bright yellow in colour. Its centre consists of zona reticularis, peripherally to which the other zones are indicated.

Pieces of suprarenal cortex are found not uncommonly on and near the kidneys, in the areolar tissue outside their capsules, within the capsule, or under it on the surface of the kidneys. They are most frequent on and around the upper pole of the kidneys and near their external border. They are rare near the lower pole.

When accessory suprarenals occur beneath the renal capsule they assume a nodular or an elongated form. Flat strips of cortex are found at the upper pole of the kidney, above whose surface they often project around their circumference (*vide* Fig. 11 (II.)). When large, they consist of a double layer of cortex, folded on itself at its margins, in which the normal zones are usually well developed. Their centre may be occupied by a solid zona reticularis with thin-walled blood-vessels. More

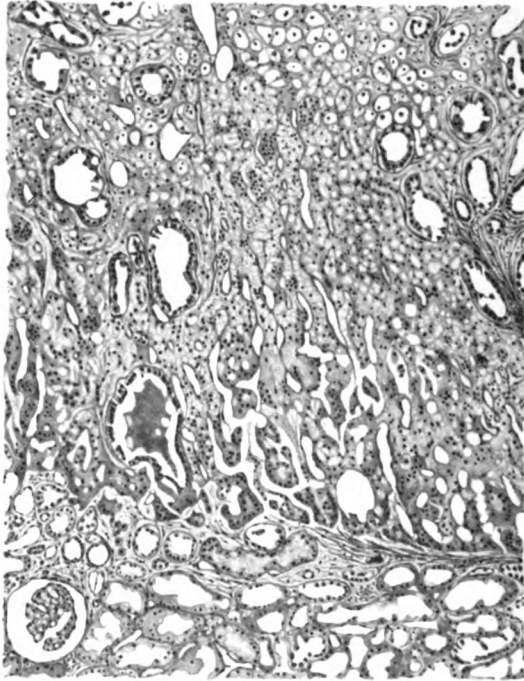


FIG. 24.

Accessory suprarenal on kidney. Inclusion of renal tubules. Magnif., 90.

frequently it consists of a series of vessels surrounded by connective tissue. These linear strips sometimes attain a large size. The biggest I have seen measures 25 mm. in length. I have seen such a strip, nearly a cm. in length, adherent to the upper pole of both kidneys of a child of four weeks.

Suprarenal medulla is said to be absent except in the nodules in the solar plexus. Fig. 23 represents a part of a linear accessory suprarenal under the capsule of the kidney at its upper pole. It was not connected with the suprarenal gland. It consists from without inwards of the usual cortical zones, the deeper part of which only appears in the figure. Next comes a



layer of deeply stained medulla, which is separated from the kidney by an irregular zona glomerulosa. Although the section has not been chromated, there can be no doubt about the medulla, since bundles of nerves, in which a few sympathetic ganglion-cells can be seen in the drawing, accompany the wide blood-vessels. These nerves are always found in the medulla, and connect it with the sympathetic.

Accessory suprarenals on the kidney are usually of the nodular form described above. They are rarely multiple. They and the linear strips are often separated from the renal tissue by a fibrous capsule, which may, however, be incomplete or absent. The suprarenal cells now come into contact with the tubules of the kidney, and grow downwards between them in the shape of groups and columns (Fig. 24). This phenomenon,

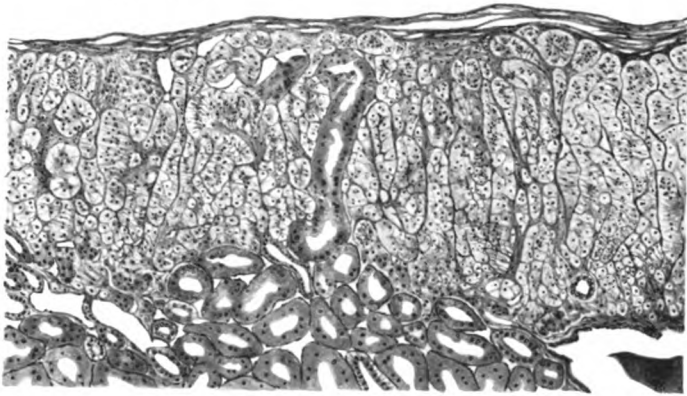


FIG. 25.

Accessory suprarenal on kidney. Ingrowth of convoluted tubule. Magnif., 80.

which will be discussed again in the next study, is merely the expression of the struggle that takes place when two kinds of epithelium come into abnormally close contact. It has nothing to do with an increased activity of the suprarenal cells due to their having originally been displaced, although it is true that they are usually victorious in the struggle for supremacy. Fig. 24 shows dilated renal tubules within the substance of the accessory organ. Besides exhibiting a tendency to form groups in every part of the specimen, every group probably representing sections of one tubule, they project above the surface of the kidney. This lies at the level of the fibrous septum in the figure, the strip of suprarenal being entirely superficial to it. These tubules can only have reached their present position by an active growth into the foreign tissue.

Fig. 25 is an even better illustration of this. A convoluted

tubule of the kidney extends almost throughout the whole of the thickness of the accessory suprarenal. Its nuclei are increased in number. Its appearance is perfectly healthy and suggests that its cells were proliferating within the foreign tissue.

I have observed these renal tubules and cysts in seven of my specimens; they appear to be not uncommon. Only once have I seen a lobulated hyaline ball, with a few flattened cells around it, which I believe to be the remains of a glomerulus, within the substance of the accessory tissue. It was situated below the level of the surface of the kidney.

One of the accessory suprarenals, which was on the surface of the kidney, had sent a narrow tongue, 4 mm. in length, downwards between the renal tubules from its deep aspect.



FIG. 26.

Accessory suprarenal on kidney. Extension into latter. Magnif., 50.

It appears to be isolated in sections, and is represented in Fig. 26. The superficial nodule would lie at a distance of about 5 cm. from the left-hand border of the drawing. The narrow process has been cut at two levels. It consists of zona glomerulosa. The centre of the larger of its two sections is occupied by a band of cellular fibrous tissue. The space on the left of the drawing is part of a wide, thin-walled vein.

I have not attempted to form an accurate estimate of the frequency of accessory suprarenals on the kidney. In my experience they are much commoner than Glynn<sup>7</sup> has found them. The above account is based on twenty-two specimens I have preserved.

In Study II. (Fig. 11) I used an accessory suprarenal on the kidney to illustrate the mode of formation of displaced tissues. In four of my specimens there is a localised patch of cirrhosis of the kidney at one or more points immediately beneath the accessory organ. Minute retention cysts are present in them

all. Eight specimens show a very conspicuous, wide, thin-walled vein, not surrounded by scar-tissue, in this situation (Fig. 26). In a linear accessory suprarenal, of which I possess serial sections, a vein extends longitudinally across the whole of its deep aspect at its centre, separating it from the kidney. These appearances suggest that the displacement was caused by an inflammatory focus, or by the presence of an abnormal blood-vessel between the suprarenal and the kidney.

Nodules of suprarenal cortex have been described under Glisson's capsule on the lower surface of the right lobe of the liver. Schmorl,<sup>25</sup> who was the first to draw attention to them, saw them on three occasions, in addition to an encapsulated tumour, which may have consisted of suprarenal tissue. In one of his cases there were three nodules; in another invasion by bile-ducts and liver-cells had taken place. I have been unsuccessful in finding them. (I have twice seen a minute rounded grey body adherent to Glisson's capsule in the suprarenal impression on the right lobe. Both of these were lymph-glands.)

Accessory suprarenals are found, below the level of the kidneys, on and close to the spermatic vein in both sexes. They are said to be much commoner in infants than in adults, and occur in the broad ligament, and on the spermatic cord. They have been seen at the hilum of the ovary and between the epididymis and the testis. According to Glynn,<sup>8</sup> who has recently investigated this question and collected the literature, no certain case of their presence within the substance of the gonad has been recorded. I have seen an accessory suprarenal, 3 to 4 mm. in diameter, among the veins of the pampiniform plexus in two cases operated on for inguinal hernia; one in a boy of eight, the other in a young adult male. Dr. P. P. Laidlaw has shown me sections of a small one on the epididymis, and of another between the layers of the broad ligament near the ovary. He found them both in fatal cases of Addison's disease. They show a marked degree of compensatory hyperplasia of their epithelium, with active growth. This is partly expansive, and in part infiltrative. Dr. Laidlaw has allowed me to make a drawing of the nodule in the broad ligament (Fig. 27). In addition to invasion of the neighbouring areolar tissue and fat, the figure shows the great irregularity in size and shape of the epithelium. Many of its cells have undergone an extreme degree of fatty change, which I have attempted to reproduce as black dots. This is not to be regarded as a primary degeneration, but as evidence of a physiological activity comparable with that which normally takes place in the suprarenal cortex, and is associated with the exercise of its functions.

The specimen proves conclusively that an accessory organ is able to respond to the needs of the body in a physiological manner, and can undergo compensatory hypertrophy when the normal tissue to which it corresponds is insufficient or has been destroyed. Far from displaying an "embryonic" organisation, accessory suprarenals are normal organs with active physiological functions. The amount of growth and invasion of their surroundings displayed by the cells of the specimen is no greater than that exhibited by a perfectly normal organ.

Except for changes like these, accessory suprarenals do not differ in structure from the cortex of that gland. We have seen

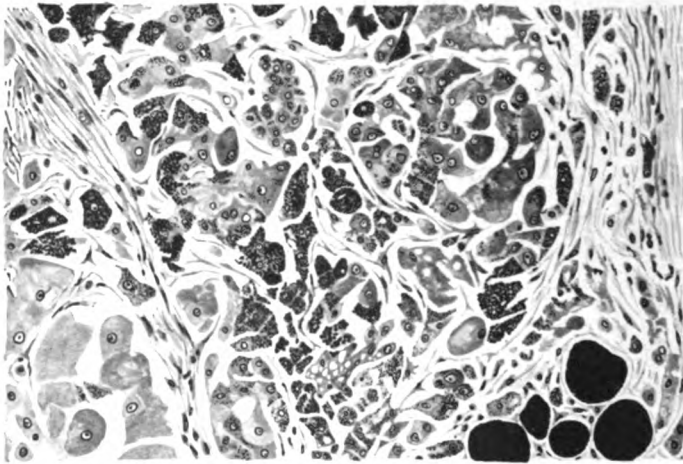


FIG. 27.

Accessory suprarenal in broad ligament. Compensatory hyperplasia in Addison's disease. Magnif., 175.

above that the latter is very liable to hyperplasia with adenoma formation. This character is shared by accessory suprarenals. Kettle <sup>11</sup> (p. 135, Fig. 80) illustrates one on the surface of the kidney. It contains an adenoma.

According to Broman <sup>3</sup> (p. 407) the cortex of the suprarenal begins its development during the fourth week of embryonic life (length of embryo = 5-6 mm.) as a series of discrete nodular thickenings of the cœlomic epithelium, which soon become confluent. Later (14-20 mm.) sympathetic cells begin to penetrate its dorso-median aspect. They give rise to the medulla. The suprarenals are at first in intimate relation with the Wolffian bodies and gonads, later (15 mm.) they come into contact with the kidneys. The right suprarenal is more or less surrounded by the liver (24 mm.).

Accessory pieces of cortex may result either from failure of one of the cœlomic anlagen to unite with the others, or from



the isolation of cortical cells by those of the sympathetic. I have attempted above to show the part that pathological adhesions play in their formation. If union has taken place with the gonad, the suprarenal cells, or some of them, are liable to be left behind at every part of the course it has taken in its descent.

Accessory suprarenals are the classic example in the body of displacement, from simple dislocation to emigration to great distances. They appear to be caused by abnormal blending of tissues, or unlawful cell union.

3. *Other heterotopic tissues in the kidneys.*—Bundles of plain muscle are not uncommonly found in the renal capsule, or

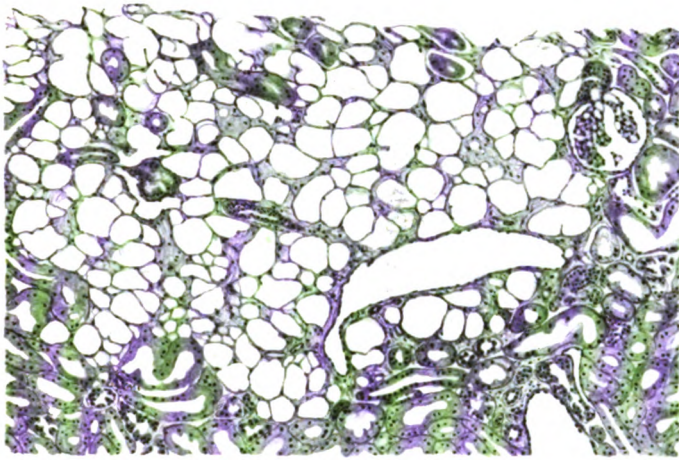


FIG. 28.

Subcapsular lipoma of kidney. (Superficial part torn away with capsule.)  
Magnif., 90.

embedded in the cortex of the organ, when they usually adhere to the capsule. They occasionally attain a considerable size and may be multiple, when they are commonly spoken of as myomata. I have seen one that measured nearly a cm. in diameter. They are the remains of the muscle fibres that are relatively abundant in the renal capsule of the fœtus. They have failed to involute, and have undergone abnormal blending with the cortex. A limited amount of independent growth has taken place in the largest specimens. They are excellent examples of hamartomata, conditions intermediate between malformations and tumours.

Lobules of adipose tissue, belonging to the perirenal fat, are of common occurrence in and under the capsule. Their ætiology is similar to that of the nodules of plain muscle. Fig. 28

illustrates one of these. It shows the orderly and perfect manner in which the adipose tissue has blended with the kidney. There are no signs of compression or atrophy of either. Incidentally it exemplifies the fact that an innocent tumour (for it would unhesitatingly be called a lipoma by most pathologists) can be perfectly unencapsulated. The wide vein near the lower part of the drawing is worthy of note.

Nodules of hyaline cartilage occur in cystic and malformed kidneys (Fig. 10 (I.)). They will be discussed below.

4. *Metanephric tubules in round ligament of uterus.*—Twisted tubules with solid glomeruli, surrounded by a fibro-cellular stroma, are sometimes found in the round ligament of the uterus. I<sup>20</sup> (Fig. 10) have described and figured one in a case

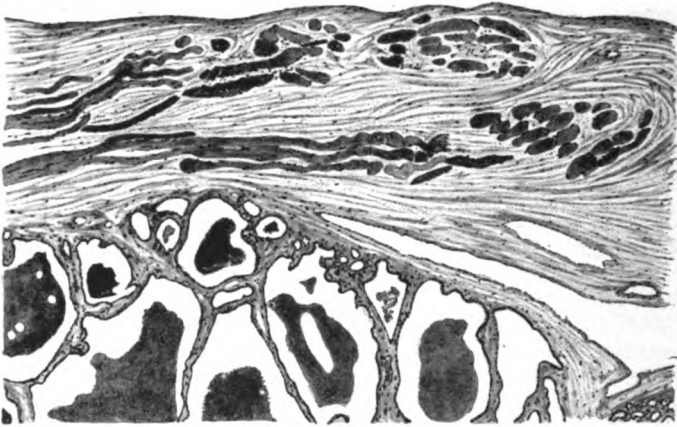


FIG. 29.

Skeletal muscle in capsule of parenchymatous goitre. Magnif., 50.

in which the left ligament was shortened and thickened. They are of importance in the causation of adeno-myomata, and are usually supposed to be aberrant Wolffian tubules. Meyer,<sup>17</sup> however, who describes one in a 23 mm. embryo, points out that the Wolffian body does not extend beyond the insertion of the round ligament, which lengthens instead of shortening, and therefore cannot drag parts of the organ caudad. The metanephros originally lies close to the inguinal canal. The aberration is caused by adhesion of a part of the renal blastema to the abdominal wall at this point.

5. *Heterotopic striated muscle.*—Fig. 29 shows a number of fibres of skeletal muscle within the capsule of a parenchymatous goitre in a girl of fourteen. With a higher power of the microscope many of them exhibit well-marked cross striation, whereas others have undergone a form of hyaline degeneration. The

capsule is fibrous and acellular. The presence of striated muscle in this situation is explained by an abnormal adhesion to one of the neighbouring muscles during the development of the capsule of the thyroid. Some of the fibres of the former were detached and incorporated within the latter.

Since the capsule is thickened as the result of the tension exerted by the parenchymatous enlargement of the gland, it is not possible definitely to exclude the post-embryonic formation of this anomaly. The acellularity of the capsule and the complete absence of signs of old inflammatory trouble within it render it probable that it is a developmental malformation. It is a typical illustration of the result of an abnormal blending of tissues.

Skeletal muscle has been recorded within the thyroid. Zielenska,<sup>29</sup> for instance, found groups of muscular bundles scattered in the broad interlobular septa of the gland in a newly born infant. They did not penetrate the capsule. She found a similar condition in the thyroid of a dog. She explains it as an abnormal inclusion prior to the formation of the capsule.

Giani<sup>6</sup> records the presence of striated muscle in the hypertrophied prostate of a man of seventy-three. The epithelium of the gland is normal. Its stroma consists of the usual connective tissue and plain muscle, and includes numerous isolated elements and groups of skeletal muscle. Tubular, oval, fusiform, and branched forms occur. There are signs of vacuolar degeneration and atrophy in some of them. Their arrangement is irregular, they occupy the greater part of the organ, and are not attached to its capsule. He concludes that they are derivatives of the sphincter urethræ, since he was unable to find transitions between them and the plain muscle of the prostate. He believes such a metamorphosis to be impossible on theoretical grounds.

It is very difficult to decide if skeletal muscle ever arises from any kind of mesenchyme cell. It appears to be developed in the embryo from the muscle plates of the mesoblast by elongation and proliferation of cells after the manner of an epithelium. This is so in the trunk and limbs, whereas in the head the conditions are somewhat different. But even here it is claimed by many embryologists that definite mesodermal muscle plates are formed. Others, however, are inclined to the view that skeletal muscle does occasionally arise from mesenchyme cells. Plain muscle arises everywhere in this manner.

Again, there is a good deal of evidence that the striped muscle of certain tumours is developed from spindle-shaped mesenchyme cells. But it is not at all certain if these striated

elements are strictly comparable with those of skeletal muscle. Simple malformations, however, can best be explained as anomalies of blending. Some of them are, indeed, incapable of another explanation.

Zipkin<sup>30</sup> records an interesting case. The left lung of a foetus of the thirty-third week is represented by a tumour, which corresponds with it in size and shape, but is not divided into lobes. It is uniform in consistency, except for the bronchi, that are present throughout. The microscope shows a cellular stroma with a preponderance of fibres and cells of striated muscle. The bronchi are normal, except that the whole of their muscular coats is represented by skeletal muscle. This condition can be explained as a case of abnormal blending, followed by proliferation of the muscle. Zipkin herself adopts this view. It is a typical hamartoma.

Schaeffer's<sup>24</sup> case bears a certain resemblance to that of Giani.<sup>6</sup> In a male foetus of the sixth month, with numerous malformations, complete aplasia of the left ureter and kidney, and indeed of the whole of the left Wolffian body, the right ureter was occluded close to the bladder, and the corresponding kidney had become cystic. Among the altered renal structures the following heterotopic tissues were found on histological examination: Solid branched masses of epithelium, whose nature is doubtful,—bundles of nerve,—lobules of adipose tissue,—fibres of plain muscle,—bundles of skeletal muscle, intimately intermingled with the renal tissue,—and nodules of a very cellular embryonic cartilage, without capsules or intercellular substance. Schaeffer derives the plain muscle from that normally present in the developing kidney, and points out the close proximity of the renal anlage to the mesoblastic somites. He regards the voluntary muscle as an inclusion within it of cells of the myotome, and the cartilage as a derivative of the sclerotome.

The only observation of this kind that I have made concerns the retroperitoneal teratoma, one of whose organs was reproduced in Fig. 1 (I.). I have omitted tumours as much as possible from these studies of malformations, but have no hesitation in making use of this one here. Teratomata are typical hamartomata, that is to say, they partake of the nature of a malformation and a tumour. The degree of differentiation and specialisation of the tissues and organs of the specimen is so great that it can almost be called an included amorphous monster. The principal feature that distinguishes it from an *acardius amorphus* is the fact that it is not covered by epidermis. This difference almost certainly depends on its environment, since it led a sheltered life within the abdomen.

The teratoma in question consists of an oval bilocular cyst, which fills the greater part of the abdominal cavity. It is



surrounded by loose areolar tissue, and receives its blood supply from the aorta by four branches that arise from its left side, in series with the intercostal and lumbar arteries. It lies in front of the aorta, and is covered by peritoneum on its anterior surface. The only spot at which it is firmly attached to the surrounding viscera is between the upper pole of the left kidney and the left suprarenal. These organs are widely separated by it. On its posterior aspect, at the apex of the curve formed by its convex right border, there is an elevated, almost spherical mass, measuring approximately 3 cm. in all dimensions. It fuses with the wall, but projects backwards. Its bulk therefore

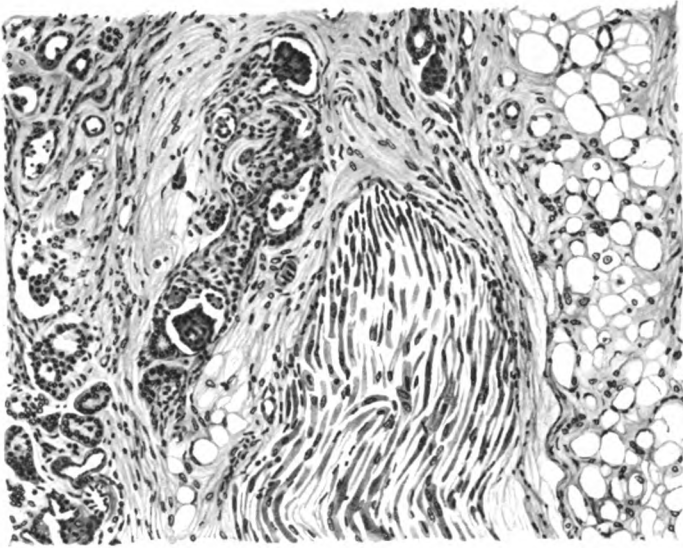


FIG. 30.

Retroperitoneal teratoma. Anomalous blending of kidney anlage, skeletal muscle, and adipose tissue. Magnif., 175.

lies outside the teratoma. It differs from it in colour and consistency, and produces the impression that it is not one of its original constituents, but that it has blended with it. Its position in regard to the attachment of the teratoma to the region of the upper pole of the left kidney is worthy of note. It is as far removed from it as the dimensions of the cyst permit.

This mass of tissue is a kidney anlage, which has blended and intermingled with the skeletal muscle and adipose tissue of the cyst wall (Fig. 30). I cannot decide if it is a part of the teratoma, or a remnant of the left Wolffian body or metanephros of the host. The cyst has obviously originated in the Wolffian body. This is shown by its attachment between the upper pole of the kidney and the suprarenal, and by its blood supply. If it had expanded within the Wolffian body and caused it to give way on its antero-lateral aspect, a fragment of mesonephric

tissue adhering to its surface here, would eventually occupy the identical position of the mass, as a result of the expansive growth of the cyst. Again, the renal tissue does not extend to the cavity of the latter, but is separated from it by a distinct zone of areolar and adipose tissue. Renal tissue has not hitherto been described in teratomata (Heijl<sup>9</sup>).<sup>\*</sup> This is, of course, no reason why it should not be present in this case as one of its intrinsic components. I have, however, not been able to satisfy myself that the secretory part of the corresponding metanephros is ever developed from the intermediate cell mass when there is complete aplasia of a ureteric bud of the Wolffian duct. My limited experience has been that, when the ureter is absent, there is no trace of the kidney, and that the severe degrees of congenital cystic kidney always possess a ureter. I have not found time to make an exhaustive search of the literature of this subject. It remains to be seen in how far the development of the ureter and kidney are correlated with each other, and if the former acts in some way as a stimulus to the formation of the latter. There are, it is true, some large cysts in the renal anlage and at its base. The former are lined by cubical epithelium which is practically featureless and gives no clue to their nature. I am inclined to regard them as dilated secretory tubules. The cysts at its base are clearly ependymal, and form part of the lining of the cavity of the teratoma. In no part of it is there a tube lined by transitional epithelium, that could be a ureter.

On the whole I incline to the view that our renal anlage is in reality a persistent part of the meso- or metanephros of the bearer of the teratoma. There is no difficulty in the way of our acceptance of this view. I need but refer to the section on persistent embryonic organs in Study II. as well as to the evidence I have collected<sup>21</sup> that parts of foetal organs that usually disappear, persist occasionally and undergo a differentiation identical in kind and degree with that of the normal tissues derived from these organs.

Whatever be its exact nature, the specimen is a typical instance of the abnormal blending of tissues. Fig. 30 shows masses of epithelium, some of which are solid, whereas others exhibit different stages of tubule formation. Glomeruli are present. They are generally solid, but some of them contain a few capillaries. Part of a bundle of skeletal muscle is represented in the figure. Its fibres are narrow, and correspond with the stage of development of the late weeks of intra-uterine life. Their nuclei are relatively large and numerous, and cross striation is well marked in some of them. A sarcolemma can often be made out with a higher magnification. The right of the drawing is occupied by adipose tissue, a few cells of which are to be seen between the muscle and the renal tissue. All

<sup>\*</sup> I take this opportunity to correct the misstatement made on p. 226 of the first of these studies.

these structures are embedded in cellular connective tissue. Other parts of the specimen exhibit splitting of muscular bundles, whose individual fibres become isolated and are often enclosed within the fat. In a few cases they surround an epithelial tubule after the manner of a *muscularis mucosæ*.

It is not difficult to interpret these appearances. One of the most constant features of teratomata is an extraordinary mingling and confusion of tissues and multiplication of organs. The only explanation of this that has been put forward to my knowledge is that the anlage of the teratoma, which clearly corresponds in its potentialities with a fertilised ovum, was disintegrated at an early stage, almost as if by the action of some explosive force. It had possibly begun to develop in an orderly manner, but sooner or later its tissues and organs were not only thrown into confusion, but were actually disintegrated. They managed to survive, however, and to undergo a surprising amount of self-differentiation. They surmounted all obstacles and differentiated into their predestined shapes<sup>21</sup> in spite of the altered conditions to which they were subjected. This hypothesis, although inherently possible, appears to me to be unsatisfactory. It pre-supposes a disruptive catastrophe, of which there is no evidence. It appears to me extremely doubtful if the anlage could recover even partially from it. Again, a degree of self-regulation of the cells is postulated which is, to me, quite unintelligible. The apparent jumbling of the anlage can, I believe, be explained in a much more satisfactory manner if we allow that differentiation is largely dependent on external influences. At one spot of the teratoma the environment will have been such as to produce a differentiation of the cells of its primitive epiblast (to take an example) into epidermis, whereas at another it will have compelled them to differentiate into central nervous tissue. This is not a pure speculation, since the histological evidence is not at all opposed to this view. It must wait, however, until we can examine the teratomata at leisure. On *a priori* grounds it appears to me to be quite sound, since it enables us to explain some of the problems of the complex teratomata on the same lines as the slight and simple tissue malformations.

To return to our specimen. If the direction taken by the differentiation of the cells of the tumour depends on their environment, there is no need to assume a passive displacement or an active migration of its muscle fibres. They simply underwent abnormal blending with the other tissues, and attained a degree of differentiation which, considering the age of the infant that carried the tumour, is wonderfully perfect.

The instances of heterotopic muscle in the literature that I

have referred to, point to the same conclusion. To take Schaeffer's <sup>24</sup> case. The myotomes and nephrotomes are parts of the primitive mesodermal segments. If one or more cells of the former became abnormally adherent to the latter, there is no reason why they should not have pursued their natural development in their midst. No displacement, active or passive, on the part of the myoblasts is necessary. They are separated from the myotome by the condensation of the developing tissues. If we assume the anomaly to have taken place at an even earlier date, before the cells of the primitive segment had undergone differentiation into sclerotome and myotome, the presence of cartilage in addition to muscle receives

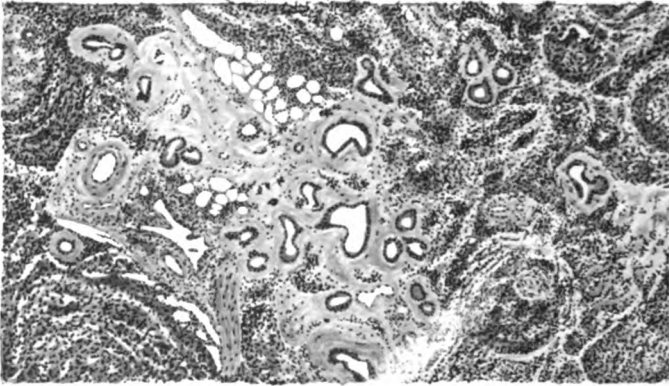


FIG. 31.

Parotid tubules in lymph-gland. Magnif., 80.

a possible explanation. It is impossible to account for the cause of the abnormal blending. It may be susceptible of an explanation similar to the one I offered for the accessory suprarenal in Fig. 11 (II.).\*

In Zipkin's <sup>30</sup> case skeletal muscle from the œsophagus may have reached the bronchi at the bifurcation of the trachea. A connecting strand of fibrous tissue is often present here, and tracheo-œsophageal fistulæ occur at this spot.

The striated muscle of the œsophagus is a derivative of the branchial muscles. Although these appear to arise as condensations of the mesenchyme of the arches in man, there is good evidence that they are homologous with the branchial myotomes of lower vertebrates. According to Edgeworth,<sup>5</sup> muscle plates are developed in the branchial arches in connection with the epithelium of the pericardium in Amphibia.

6. *Epithelial inclusions in lymph-glands.*—Fig. 31 represents

\* On the other hand, it may be nothing more than an abnormal differentiation.

the appearance seen in the hilum of a small lymph-gland under the capsule of the parotid in a woman of twenty-five. The hilum is fibrotic and contains a number of tubules, many of which are dilated. They are lined by cubical epithelium, whose cells tend to form two rows. Most of them are surrounded by a thick hyaline connective tissue tunica propria. A few tubules are found within the general parenchyma of the gland. It was encapsulated and connected with the parotid only by areolar tissue. I have seen identical tubules in a tuberculous præ-parotid lymph-gland in a child of eighteen months.

These tubules have the same structure as the smaller ducts of the parotid, especially when they are surrounded by hyaline envelopes in chronic inflammations of the gland. They have become separated from the parotid and enclosed by the lymphoid tissue.

Lymphatic glands are developed in the following manner: A plexus of lymphatic vessels is formed at their future site. This is followed by a diffuse infiltration of lymphocytes around the small arteries and capillaries that occupy the meshes of the plexus. They increase in number and are condensed to form the lymph-nodes. The plexus gives rise to the sinuses of the gland. Neisse<sup>18</sup> has shown that in a foetus of 120 mm. there are numerous lymph-nodes within the parotid, and at a later stage in the submaxillary as well. Their outlines are diffuse, and they contain salivary tubules. When condensation and capsule formation take place and these nodes develop into the præ-parotid lymph-glands, it usually happens that the tubules are separated from the rest of the parotid. In all the newly born infants this writer examined he was able to demonstrate the presence of from eight to ten nodes and lymph-glands, all of which contained scattered acini, or whole lobules with ducts, of salivary tissue.

These included parotid tubules result, therefore, from an abnormal blending of tissues. There has been no active displacement. Their inclusion within lymph-glands is due to the growth of the latter and the formation of a capsule.

Tubules, lined by columnar ciliated epithelium, and often surrounded by envelopes of cellular stroma, have been recorded within the aortic and iliac lymph-glands by several observers (*e. g.* Wuelfing<sup>28</sup>). They are generally believed to be tubules of the Wolffian body.

7. *Heterotopic cartilage*.—Nodules of cartilage have been described not infrequently in malformed and cystic kidneys. The case of Schaeffer<sup>24</sup> described above is typical of them. One of these nodules, surrounded by a perichondrium and consisting of very cellular young hyaline cartilage, is reproduced in Fig. 10 (I.). It was found in the cystic horse-shoe kidney of

a symelian monster, These structures are usually regarded as inclusions of cells of the sclerotome resulting from an anomaly of development. They have been named "choristomata" \* by Albrecht,<sup>1</sup> who defines them as "structures that can with certainty be assumed to be displaced parts of organs, and that give the impression of a tumour, on account of their abnormal position and their definition and isolation from the surrounding tissues." They are most frequently met with in malformed kidneys, but have been recorded from other parts of the body as well; *e. g.* in the parotid of an infant by Lubarsch.<sup>14</sup>

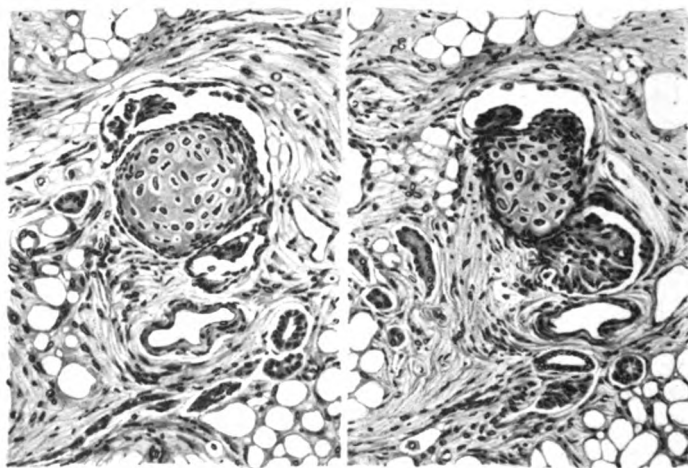


FIG. 32.

Retroperitoneal teratoma. Nodule of cartilage between two glomeruli. Magnif., 190.

I must again make use of the retroperitoneal teratoma already described. Here again it is the kidney anlage that we turn to. Fig. 32 represents two views of a rounded nodule of cellular hyaline cartilage, which lies between a pair of glomeruli, into the Bowman's capsule of the upper one of which it projects. It is surrounded by an irregular cambium, which forms a perichondrium to it, and is thickest where the nodule projects into the capsule. The upper glomerulus is atrophied and flattened throughout the series of sections, whereas the lower one has reached a degree of development as great as that attained by any of them in the specimen (*vide* Fig. 30).

The glomeruli of the kidney are developed in pairs. The ureteric diverticulum of the Wolffian duct is capped by a mass of mesoblast. The former undergoes a series of dichotomous

\* From  $\chi\omega\rho\iota\zeta\omega$ , separate (chorizoma would therefore have been better).

divisions to form the collecting tubules, and the caps of mesoblast follow suit. These become hollowed out into S-shaped metanephric tubules, whose lower limb (the one nearest to the hilum) expands over the other. Its concavity becomes vascularised and forms the glomerulus. The proximal limb of the S joins the collecting tubule and is twisted into secondary loops. The metanephric tubules thus open into the collecting tubules in pairs.

The pair of glomeruli figured, together with the few tubules that surround them, occupy a very isolated position in the anlage, being separated from the nearest mass of nephric epithelium by a thick layer of areolar and adipose tissue and muscle. I have expressed my uncertainty as to whether we are dealing with meso- or metanephros. There can be no doubt, however, that this particular pair of glomeruli has been developed after the manner of the kidney.

The nodule of cartilage is placed in the concavity of the upper loop of the S of the left (or upper, in the figure) of a pair of tubules. It has obliterated the proximal ends of both tubules. The glomeruli are displaced inwards and approximated to each other on account, no doubt, of the pressure exerted on Bowman's capsules by the nodule.

The presence of the cartilage at this spot can be explained in one of two ways. Cells of the sclerotome of the teratoma have undergone abnormal blending with the kidney anlage, and been surrounded by it during its growth. Or, the cartilage has arisen *in situ* as a result of an abnormal differentiation undergone by some of the cells of the anlage.

Three facts appear to me to favour the latter view :—(1) The otherwise complete absence of cartilage in this part of the cyst. (2) The intimate relationship of the nodule with one of the pair of glomeruli. (3) The fact that the centre of another glomerulus is occupied by a translucent matrix, in which there are a few widely separated cells. The stage of development of the cartilage, if such it be, is not sufficiently far advanced in this case to warrant the statement that the matrix is definitely cartilaginous. A slightly more advanced, but still ambiguous structure was seen, surrounded by a ring of epithelial cells, clearly tubular in character.

The presence of a perichondrium in Fig. 10 (I.) and Fig. 32 proves no more than that active proliferation was taking place. It is strictly comparable with the cellular periosteum associated with heterotopic bone in calcified necrotic foci, which <sup>19</sup> results from the stimulation of ordinary fibroblasts by an excess of calcium salts. The perichondrium in these cases does not, to my mind, prove that the cartilage is a derivative of the sclerotome.

Nodules of hyaline or of elastic cartilage occur in the capsules

of the tonsils. They have given rise to much argument. By some they are regarded as derivatives of the second branchial cartilage or its perichondrium, by others as the result of chronic inflammation. The nodules are often bilateral, they undergo ossification and are replaced by bone.

Ruckert <sup>23</sup> always found a perichondrium. Often there were no signs of inflammation. In forty-eight tonsils of fœtuses and infants he examined, he found cartilage seventeen times, four times in both tonsils. He concludes that its presence is due to a developmental anomaly. I have seen multiple nodules of both kinds of cartilage in the tonsils of three cases, as well as spicules of dense bone in a man of sixty-one. They were found in adults of from twenty to twenty-nine, and were associated with chronic inflammation and hyperplasia of the organ, and with fibrosis of its capsule. The latter contains bands of very dense fibrous tissue. The cells at their centres are gradually converted into cartilage cells. A perichondrium is invariably absent. In one case a fibrous band contains minute lobules of adipose tissue, around one of which conversion of fibroblasts into young cartilage cells is taking place. This appears to me to be clear evidence of its origin *in situ* as the result of fibrosis. The fact that the nodules are scattered in all parts of the capsules supports this view.

It will be well to produce all the evidence of the formation of cartilage *in situ* from the connective tissue, although it should more properly be discussed in the next study. This tissue has been found in a variety of purely inflammatory conditions, in which it is generally associated with bone. I have recently described such a case,<sup>21</sup> and have collected a number of references to this condition. It has most frequently been recorded in sclerotic arteries.

Marburg <sup>15</sup> has described an arteritis cartilaginosa of the cerebral vessels, which appears to result from mucoid degeneration of their stroma. I <sup>20</sup> have seen cartilage in a sarcoma of the body of the uterus. The cells were separated by mucin, acquired capsules, and took on the characters of cartilage cells (*vide* Fig. 7 of my paper). I believe that the formation of cartilage, which after all is the living tissue in the body whose cells are surrounded by a mucoid stroma, is occasionally the end result of a mucoid degeneration. We shall see that certain tumours of the salivary glands support this view.

I believe that there is a good deal of evidence that heterotôpic cartilage, in infants as well as in adults, does not invariably result from inclusion of cells of the sclerotome. On the contrary, many instances of its occurrence can readily be accounted for as anomalies of differentiation of the cells of the affected tissue.



Nearly all the anomalies that have been described in this study are characterised by a more or less pronounced degree of displacement of a tissue. Meyer <sup>16</sup> has clearly and convincingly demonstrated that it is impossible for the cells of a developing organ to transport a foreign cell, not to mention a group of cells, to a distance. He uses the Wolffian duct as his example, and shows that it increases in length by means of continuous division of its apical cell. Each daughter cell, as it is formed, is obliged to feel its way between those of the mesenchyme and under the epiblast. It glides into and occupies the available space between these cells. It is a very delicate structure, and does not possess the force to thrust them aside. Far less is it able to propel them forward, should it have become adherent to one of them. Should this have happened, the abnormally blended cells will remain *in situ*, and growth of the duct caudad will be deflected. Displacement, when it happens, is and must be purely passive. It is brought about by proliferation of neighbouring cells of the tissue itself, or of the mesenchyme in capsule formation, or by the intercalation of another tissue or organ between the displaced cell and the tissue from which it has sprung. This result is also brought about by the shifting of an organ on account of unequal growth of other tissues. The classic example of this is the descent of the gonad and the displacement of pieces of the suprarenal cortex in its path. The only anomaly that has occurred, and that is responsible for the displacement, is the abnormal relation that has been established with the neighbouring cells.

This observation of Meyer helps us to form a correct idea of how Brunner's glands in the stomach or in the distal end of the vitelline duct when it remains patent, and numerous other anomalies of a similar nature, have been brought about. They are not displacements in any sense of the word, but anomalies of differentiation. I need not discuss them here, as I have recently <sup>21</sup> gone into the manner of their production.

This finishes what I have to say on the subject of congenital tissue malformations. Their cells always undergo a high degree of differentiation, which but rarely falls short of that attained by those of the corresponding normal organs. The clearest evidence of this is afforded by their ability to react in a physiological manner to the demands made on them when the functions of the latter are impaired. The amount of proliferation they display is always proportional to their high degree of differentiation, and is therefore not appreciably in excess of the normal. These facts appear flatly to contradict the postulates of Cohnheim's theory. It therefore becomes necessary to inquire

into the frequency of tumours whose structure compels us to assume that they must have originated in congenital tissue malformations or "cell-rests," and for which no other explanation is possible. Before doing this, however, I propose to discuss certain other tissue malformations, many of them almost identical in appearance with the congenital ones, that have originated after development was completed.

#### CONCLUSIONS

The heterotopic tissues examined in this study are all, in so far as we can form an opinion of their causation, the results of abnormal blending of cells, followed by a varying amount of displacement in some cases.

Displacements are never brought about by active movement of cells. They are produced passively by growth and multiplication of cells, capsule formation, and shifting due to unequal growth.

Dislocations, on the basis of developmental anomalies, can occur in post-embryonic life.

Displaced cells can functionate. In this respect they do not differ from normal tissues.

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## ESTIMATION OF CHLOROFORM IN THE BLOOD AFTER DEATH

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FROM time to time fatalities occur under chloroform anæsthesia, and in spite of full investigation of the circumstances attending the administration of the anæsthetic and a post-mortem examination of the body, the precise cause of death is frequently a matter of probability only and not established fact. This undesirable state of affairs is due, in part, to the lack of exact information with regard to certain important particulars. One question of great importance in nearly every case is the amount of chloroform in the body at the time when death ensues. It has been the custom to assess this from the amount of anæsthetic used during the whole administration, allowing for time, method of anæsthesia, and so on. But clearly the amount of chloroform taken into the body need not bear any exact relationship to the amount distributed on a mask; and we felt that it would be a considerable advance if some reliable method could be devised by which the amount of chloroform in the dying body could be determined by estimation of chloroform after death.

What we really desire to know is, the precise amount of chloroform at the time of death in the more important centres of the body, such as the brain and heart. There are many and probably insurmountable difficulties in the way of obtaining this particular information; but what we know with regard to the distribution of chloroform in the body during anæsthesia indicates that the anæsthetic is absorbed through the lungs into the blood, and distributed to the tissues according to its relative solubility in the various tissues. A determination of the amount of chloroform in the blood at the time of death would therefore be an indirect estimate of the amount in the vital centres.

Chloroform is a relatively stable substance and it is not, so far as we are aware, decomposed by the tissues of the body to any great extent, though there is evidence that some destruction

occurs in the liver.<sup>1</sup> It would therefore seem probable that it is not decomposed in the body after death and that it should be possible to recover it quantitatively, even after the lapse of two or three days. If this proved to be the case, the amount of chloroform in the heart blood post-mortem should be a measure of the amount in the vital centres at death, and should settle the vexed question of over-dosage in many cases. In the literature there are not many estimations of this kind,<sup>2</sup> and these did not support the argument, but as they were carried out by older methods we undertook some experiments to test the point. Our results are of considerable interest, but they do not prove all that could be wished.

#### METHODS

Rabbits were used as experimental animals. They were anaesthetised throughout with chloroform. Tracheotomy was performed after induction of full anaesthesia in order to obviate any asphyxial factor, and to render the continuation of deep anaesthesia simple. Deep chloroform anaesthesia (loss of corneal reflex) was maintained as a rule for thirty minutes, and death then brought about by gradual over-dosage. The animals were thus partially saturated with chloroform, and recovery of the chloroform should have been facilitated. Immediately after death about 10 c.c. of blood were removed from the right side of the heart through a cannula pushed down the right external jugular vein. This sample was used to determine the concentration of chloroform in the blood at the time of death.

After removing the cannula the jugular vein was tied off, the tracheotomy tube cut away, and the carcass kept in a cool place for two or three days. As the experiments were done in the winter there was little decomposition, and this may have influenced our results, but the conditions were comparable to those existing when a body is kept in a refrigerator. After the storage period post-mortem blood was collected in the following manner. The thorax was laid open widely, the inferior vena cava, the superior vena cava, the pulmonary artery, and the aorta were tied. The thoracic viscera were then excised as a whole, and held by the lungs, heart dependent, over a glass basin which had previously been weighed. All chambers of the heart were then laid open in turn, and the whole of the serum and clot collected in the basin, which was weighed again. As a rule 8 to 10 grms. were obtained. This procedure was adopted in order to get both fluid and cells in as fair proportion

as possible, since it is known that chloroform is always present in greater amount in the cells than in the fluids.<sup>3</sup>

The estimations of the chloroform were all done by Nicloux' <sup>4</sup> method with one slight modification. The venous blood, collected in a pipette lined with oxalate, was allowed to run into a clean Jena flask, previously weighed, containing 5 c.c. of 5 per cent. solution of tartaric acid in ethyl alcohol, and about 20 c.c. of alcohol previously distilled over lime. The contents of the flask were gently agitated as the blood was added, in order to obtain a fine granular precipitate and lake all the red corpuscles. The flask was weighed again. About 80 c.c. of pure ethyl alcohol were then added, and approximately 70 grms. of alcohol containing the chloroform distilled off into another Jena flask, which contained a little alcohol and sodium ethylate. This is the only modification of the Nicloux method, and it is much more convenient than securing chlorine-free caustic alkali. The ethylate was made fresh for each estimation by adding 0.3 gm. sodium to the alcohol in the flask used as a receiver, dissolving, and cooling.

The distillate and the ethylate were then boiled under a reflux condenser on the water bath for at least one and a quarter hours. The alcohol was distilled off, the residue dissolved in dilute nitric acid (1.5 c.c. nitric acid in 10 c.c. water) and exactly 5 c.c. of N/10 silver nitrate added. The silver chloride was coagulated by boiling, filtered off, the precipitate and flask washed six times with hot distilled water, and the excess of silver estimated in the filtrate by titration with N/100 ammonium sulphocyanate, using iron alum as an indicator.

In the case of the post-mortem clot, it was found necessary to break it up as finely as possible in order to get satisfactory results. This was readily effected by grinding it finely with the tartaric acid first, and later the resultant paste with successive quantities of alcohol. Manipulation of blood or blood clot with exposure to air was necessary, but it has been shown that chloroform is only slowly lost by blood even in a vacuum.<sup>5</sup>

The estimations of chloroform went quite smoothly by this method once it was realised how important it was to get all the red cells destroyed by the tartaric acid, and we are convinced that the method is wonderfully accurate, even on less than 10 c.c. of blood, and further that, under the conditions of our experiments, the figures for the volatile chlorides obtained represent chloroform and chloroform alone.

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### RESULTS

The accompanying table shows the results of seven experiments carried out along these lines and one control. It will be observed that in all cases the percentage of volatile chloride recovered from the heart blood post-mortem is greater than that in the blood at the time of death.

VOLATILE CHLORIDES IN THE BLOOD, CALCULATED AS CHLOROFORM AND EXPRESSED IN MILLIGRAMMES PER HUNDRED GRAMMES \*

Exp.	At death.	After death.	Interval.
1	34.56	37.85	2 days.
2	†22.5	34.29	2 „
3	56.76	80.91	3 „
4	59.36	64.12	2 „
5	61.52	66.22	2 „
6	47.63	54.31	2 „
7	58.6	62.97	2 „
8	0.0	0.0	2 „ Ether control.

With the exception of the second experiment, in all the instances in which the body was kept for two days there is approximately a proportional increase in the amount of chloroform found post-mortem, and since this increase was unexpected and constant it required explanation. We do not believe that it is experimental error; and the control, where a rabbit was killed with ether after a period of ether anæsthesia, shows (a) that all apparatus and reagents were chlorine-free, and (b) that no detectable volatile chloride is formed on keeping the body for two days after death.

In Experiment 8, where the body had been kept for three days, it was observed that the contents of the heart were very firm and consisted almost entirely of clot with very little serum. This suggested, what is demonstrated by other data below, that fluid leaves the vascular system slowly after death. Since most observers state that the greater proportion of the chloroform is carried by the red cells, it is clear that if fluid leaves the heart and vessels, the chloroform content of the clot will inevitably rise. The striking increase in the chloroform content of the heart blood after death recorded above would appear to be capable of being explained along these lines. We hoped to verify

\* In the early experiments the body was hung head downwards during storage and in the later experiments the body was left horizontal. The position of the body during storage did not appear to make any material difference in the results.

† Unexpected cessation of respiration and early death; artificial respiration for one minute.

this, to correct the figure for the post-mortem blood by estimating the hæmoglobin in the blood at death and at the post-mortem, and so correct for the increased concentration of the cells.

We succeeded in estimating the increased concentration of cells in four experiments indirectly, through the pigment content of the samples of blood, or clot and serum, which were employed for chloroform estimation. The following procedure was adopted. Excess of 10 per cent. aqueous sodium hydroxide was added to the contents of each flask, from which the chloroform and alcohol had been distilled, the flask having been warmed on the water-bath for some hours. The whole of the blood pigment was thereby converted into soluble alkaline hæmatin and the proteins destroyed. The brown solution was diluted largely with water and a small excess of acetic acid added to precipitate the hæmatin. In each case the hæmatin was collected, washed with hot water, dissolved in acidified alcohol, and the resultant brown solutions were compared by means of a Dubosc colorimeter.

The following results were obtained—

RELATIVE HÆMOGLOBIN CONTENT OF BLOOD

Exp.	At death.	After death.
4	100	125
5	100	150
6	100	180
7	100	126

These indicate clearly that there is striking concentration of the cells in the vascular system and loss of fluid on keeping a body for two days. The explanation of this passage of fluid out of the vessels is not very important for our immediate purpose, but is probably due to the formation of acids in the asphyxiated tissues at death, the formation of simple substances by autolysis, and the loss of integrity of the endothelial lining of the vascular system, as the cells composing this limiting membrane die and degenerate. But whatever the true explanation may be, it is clear that the chloroform content of the blood after death should always prove to be higher than that of the blood at death, and further, the difference theoretically expected is amply sufficient to account for the difference found experimentally, if it is assumed that 70 per cent. of the chloroform in blood is normally carried by the red cells. This assumption appeared to be justified by the available data,<sup>3</sup> but we tested the point in Experiments 5, 6, and 7.

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In Experiments 5 and 6 a second 10 c.c. sample of blood was taken into oxalated pipettes, distributed in centrifuge tubes, and the chloroform content of the red cell layer estimated in addition to estimations on whole blood. The difference in the chloroform content of the red cell layer of 100 grms. blood and 100 grms. whole blood gave the amount in the plasma layer separated by the centrifuge. Haematocrit determinations gave the true relative volume of cells and plasma, and from these the relative weights could be determined, and the true distribution between cells and fluids calculated. The increase expected in the post-mortem clot could then be estimated, by adding the amount calculated as due to increased red cells, and subtracting an amount calculated for plasma loss. The following are the results—

Exp.	Mgm. chloroform per 100 grms. blood at death.	Distribution of chloroform between cells and plasma.	Percentage chloroform in red cells.	Relative number of red cells at death and after death.	Mgm. chloroform expected in 100 grms. PM blood.	Mgm. chloroform found in 100 grms. PM blood.
5	61.52	41.24 : 20.28	67	100 : 150	77.1	66.22
6	47.63	37.08 : 10.55	77	100 : 180	73.82	54.31

Comparison of the last two columns of figures shows that the increase in chloroform content expected, owing to the concentration of cells which occurs post-mortem, is greater than the amount actually found experimentally. In other words, we must conclude that in addition to loss of fluid from the vascular system after death, there is also a loss of chloroform; and that this is greater than can be accounted for by that amount dissolved in the fluid which transudes from the vessels.

The results obtained in these experiments by calculation were confirmed in another way in Experiment 7. In this instance samples of blood at death and after death were separated into cells and fluids by centrifugalisation, and the four fractions thus obtained worked up separately.

### MGM. CHLOROFORM

At death.		After death.	
In 100 grms. of plasma.	In 100 grms. of cell layer.	In 100 grms. of serum.	In 100 grms. of clot.
22.2	93.2	19.4	86.1
In 100 grms. of whole blood. 58.6		In 100 grms. of whole blood. 62.97	



It will be observed that there is a greater concentration of chloroform in the plasma and in the cells at death than in the serum and the clot respectively after death. The whole blood figures are similar to those of previous experiments. Hæmatocrit determinations of true cell volume were not done in this case, but if the cell volume was about 30 per cent., then a chloroform concentration of about 75 mgrms. per 100 grms. blood was to be expected post-mortem instead of the 62·97 found. Even taking the imperfectly separated cell layer and assuming the deposit to be solid cells, a figure of 68·5 should have been obtained in the post-mortem specimen. In this last experiment the loss of chloroform is further shown by the occurrence of appreciable hæmolysis which should have caused an increase.

We regard the loss of chloroform as due to a redistribution of this substance in the body and not to destruction. Destruction appears to us unlikely to occur in view of the known stability of chloroform, while, on the other hand, the facts that decomposition of the cells takes place and that fluid moves about in the carcase make it likely that the solubility of chloroform will vary with the decomposition and will diffuse about the body in a similar manner to the fluids. Whether we are right on this point or not, there can be no doubt that the concentration of chloroform in the heart blood found post-mortem is not a measure of the amount which existed in the circulating blood at the time of death.

Further, we regard the condition of partial saturation of our animals with chloroform as minimising the redistribution factor; and as about half the fatalities under chloroform take place before deep anæsthesia has been established, and therefore in unsaturated bodies, there is the less hope of post-mortem assays proving of practical importance in investigating deaths under chloroform anæsthesia.

It appears to us that if exact information is to be obtained with regard to the chloroform concentration in any given case, the estimation must be carried out on blood collected at the time of the fatality. This could easily be done if in every case in which dangerous symptoms appeared, it was made a routine to collect venous blood from an arm vein. Cases which recovered after dangerous symptoms would yield a series of figures indicating the maximum recoverable dose, and cases of non-recovery would yield figures indicating the lethal dose. The interpretation of the figures would not be perfectly straightforward, because the relative number of red cells would influence the results, increasing the total amount when these were

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numerous and diminishing it when few. Probably the ideal procedure would be to determine the partial pressure of the chloroform in the blood, and it is suggested that it is desirable to carry out experiments with this object in view.

### CONCLUSIONS

The amount of chloroform found post-mortem in the heart blood of animals which have been killed by over-dosage after a period of full anæsthesia is no exact measure of the amount existing in the blood at the time of death.

The amount of chloroform is modified by loss of fluid from the vascular system and retention of cellular elements, decomposition of cells (hæmolysis, etc.), and redistribution of chloroform in the body.

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## TESTS FOR PHYSICAL EFFICIENCY \*

### PART II

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IN a previous paper † evidence was given that the reaction of the pulse to exercise was a good indication of the physical fitness of the subject. The ratio between the pulse-rate for the two minutes immediately following the given exercise and the pulse-rate at rest, "the pulse ratio," was taken as a more convenient and better indication of the reaction than a determination of the time taken for the pulse to return after exercise to its original frequency. The exercises consisted in walking or running up and down stairs, and were graduated from 1492 to 3730 and 5476 kilogrammetres for a man weighing 68 kilos, each exercise lasting five minutes. This form of exercise was selected because it is one to which all subjects are accustomed. It was recognised that the results of the test might vary with the external conditions and the nature and amount of the muscular work performed; for this reason a further series of experiments has been made.

In the first place it was necessary to consider observations upon the range in the rate of the pulse of the same individual at rest. The following tables give the results for men and women (Tables I. and II.).

The largest individual range of pulse-rate at rest for 18 men is 36, while the corresponding figure for 18 women is 57.

We have collected also a number of single observations upon the pulse of male medical students, and of women students

\* Expenses in connection with this research were defrayed in part by a grant from the Medical Research Council.

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TABLE I.  
AVERAGE AND RANGE OF PULSE-RATES FOR RESTING SUBJECTS (MEN).

Subject.	Number of days of observation.	Average.	Range.	Time.	Remarks.
R.A.M.C. { C. M. J. A. Cn. N.	7 8 7 7 7 7	89.6 74.6 81.3 84.3 77.1 75.4	77-98 <sup>21</sup> 63-87 <sup>24</sup> 58-92 <sup>24</sup> 62-98 <sup>26</sup> 58-85 <sup>27</sup> 65-84 <sup>19</sup>	July 1906 9-10 a.m.	Observations on soldiers taken by L. E. L. P. and M. S. P. as part of work of Committee on Physiological Effects of Food, Training, and Clothing of the Soldier.
1st Batt. Yorks. { D. Ca. T. B.	12 12 12 12	78.3 86.4 82.7 81.5	70-90 <sup>20</sup> 78-100 <sup>22</sup> 72-92 <sup>20</sup> 72-90 <sup>18</sup>	Aug., Sept. 1906 9-10 a.m.	
Royal Irish Fusiliers { A. B. C. D.	10 10 10 10	75.6 97.0 75.2 59.4	66-84 <sup>18</sup> 88-104 <sup>14</sup> 68-90 <sup>22</sup> 52-72 <sup>20</sup>	Aug., Sept. 1906 9-10 a.m.	
Investigators { M. S. P. T. F. B.	33 10	81.3 72.6	68-96 <sup>28</sup> 66-82 <sup>16</sup>	3 p.m. Nov. '06, March '07	
E. C. W. W. D. H.	8 4	68.9 57.6	57-77 <sup>20</sup> 53-68 <sup>15</sup>	June 1922 March and June 1922	42 observations. 8 observations.

TABLE II.  
AVERAGE AND RANGE OF PULSE-RATES FOR RESTING SUBJECTS (WOMEN).

Subject.	Number of days of observation.	Average.	Range.	Time.	Remarks.
U.	5	63.4	56-78	3 summer, 2 winter	At Chelsea Physical Training College.
G.	4	77.5	72-84	2 summer, 2 winter	
M.	8	75.2	65-82	5 summer, 3 winter	
W.-C.	4	59.2	57-62	Nov.-Feb.	
H.	3	76.6	72-85	November	
W.	5	69.6	56-83	Nov.-Feb.	
V. S. M.	2	72.5	70-75	Nov.-Dec.	
I. H.	3	85.7	81-91	November	
S.	10	67.0	61-79	6 summer, 4 winter	Untrained
B.	12	75.4	71-80	6 summer, 6 winter	
C.	3	66.0	62-70	Feb.-March	Unfit
D. H.	7	78.1	64-90	May.	
E. B. G.	7	77.8	65-109	"	
R.	7	74.6	66-84	"	
T.	5	81.6	66-100	"	
M.	4	79.5	71-87	2 May, 2 Dec.	
C. B.	9	76.6	58-115	May.	Includes 6 observations a day for 6 days. Total, 39 observations. 12 observations in very hot weather.
K.	8	79.8	55-90	"	

Department of Remedial Exercises, Guy's Hospital.

Department of Remedial Exercises, Guy's Hospital.

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in the Department of Remedial Exercises, Guy's Hospital, and at Chelsea Physical Training College (Table III.).

TABLE III.  
AVERAGE AND RANGE OF PULSE-RATES FOR GROUPS OF MEN AND WOMEN.

Average.	Range.	Number of subjects and observations.	Remarks.
Men { 83·4 79·4 70·1	52-104 58-98 52-106	109 on 8 soldiers and M. S. P. (4 soldiers 1st Batt. Yorks., 4 of R.I.F.) 43 on 6 R.A.M.C. privates. 254 on 79 medical students.	Observations by L. E. L. P. and M. S. P., 1906.  Recent observations at Guy's Hospital.
74·7	52-106	406 observations on 94 men.	General Averages for Men.
Women 79·5	53-116	103 on 103 women students of Massage and Remedial Exercises.	Recent observations at Department of Remedial Exercises, Guy's Hospital and Chelsea Physical Training College.

The average of 406 observations on 94 men is 74·7 with a range from 52 to 106; of 103 observations on 103 women, 79·5 with a range from 53 to 116. In these figures are included no cases in which illness was present. The subjects were engaged in their ordinary duties, but it is possible that minor ailments were sometimes overlooked both by the subject and the observer.

These data indicate the necessity for greater recognition of the range of the pulse-rate in healthy subjects at rest, for, as

TABLE IV.  
PULSE-RATE IN RELATION TO BODY WEIGHT AND SURFACE AREA.

	Weight of body in kilos (net).	Number of subjects.	Pulse.		Surface area * (in sq. metres).		
			Average.	Range.	Average.	Range.	Number of subjects.
Men.	45-50	4	76·0	63-90	1·48	1·46-1·50	2
	50-55	7	75·4	58-101	1·59	1·53-1·64	4
	55-60	17	77·0	65-98	1·69	1·58-1·82	10
	60-65	18	73·6	54-100	1·76	1·72-1·82	10
	65-70	15	70·7	52-93	1·81	1·77-1·86	7
	70-75	7	69·9	61-84	1·88	1·81-1·97	7
	75-80	10	71·1	57-86	1·97	1·92-2·02	4
	80-85	2	68·5	53-84	2·13	—	1
Women.	45-50	4	81·7	68-116	1·45	1·40-1·51	4
	50-55	11	79·8	57-100	1·58	1·53-1·63	8
	55-60	12	77·0	59-109	1·59	1·54-1·63	11
	60-65	7	72·8	60-91	1·75	1·69-1·81	4
	65-70	3	78·3	62-86	1·74	1·72-1·76	3
	70-75	1	63·4				

\* Calculated on Du Bois' formula:  $S = .007184 \times W^{0.425} \times H^{0.725}$  where S is the surface in square metres, W the weight in kilogrammes, and H the height in centimetres.

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in the case of temperature and other physiological processes, there is no definite normal for the pulse. The causes of variations are by no means simple, and have not been especially investigated in this research; we may, however, draw attention to the following factors—weight, athletic training, age, temperature of the body, external temperature, and time of day.

These figures show that the average rate of the pulse is lower in the heavier individuals, men or women, as the case may be. Weight, however, is not the factor so much as the relation between surface and mass. The exchange of material and the production of heat are relatively greater in the small than in the big, warm-blooded animals. The pulse in the subjects at rest may be an indicator of the rate of the exchange of material, but a discussion of this question must be postponed until the other factors have been considered.

TABLE V.

AVERAGE RATE AND RANGE OF PULSE DURING REST FOR GROUPS OF STUDENTS, CLASSIFIED ACCORDING TO DEGREE OF PHYSICAL TRAINING.

Trained.			Untrained.			Unfit.			Remarks.
Average.	Range.	Number of subjects.	Average.	Range.	Number of subjects.	Average.	Range.	Number of subjects.	
75.2	53-96	51	83.9	60-116	52				Women Students. Chelsea Physical Training College. Guy's Hospital, Department of Remedial Exercises. Under 25 years of age. 25-30 years of age. Over 30 years of age.
75.9	53-91	21	85.3	60-116	12				
72.1	65-82	2	83.4	62-115	6				
70.0		1	78.1	67-98	7				
71.5	63-91	4	76.4	66-88	7	82	74-90	2	Men, Medical Students, 16-20 years of age. 20-25 years of age. 25-30 years of age. Over 30 years of age.
64.1	54-78	10	75	53-102	21	84	73-101	5	
61		1	70.1	60-84	7	67		1	
63.7	58-68	3							

The rate of the pulse of trained individuals at rest is definitely lower than that of the untrained. This is shown by both the averages and the ranges already quoted (Table V.); the trained men have an average rate of 61, the untrained 72, and the unfit 81; and in the case of women the average is 75 for the trained and 84 for the untrained.

In the same table it is shown that the rate of the pulse of

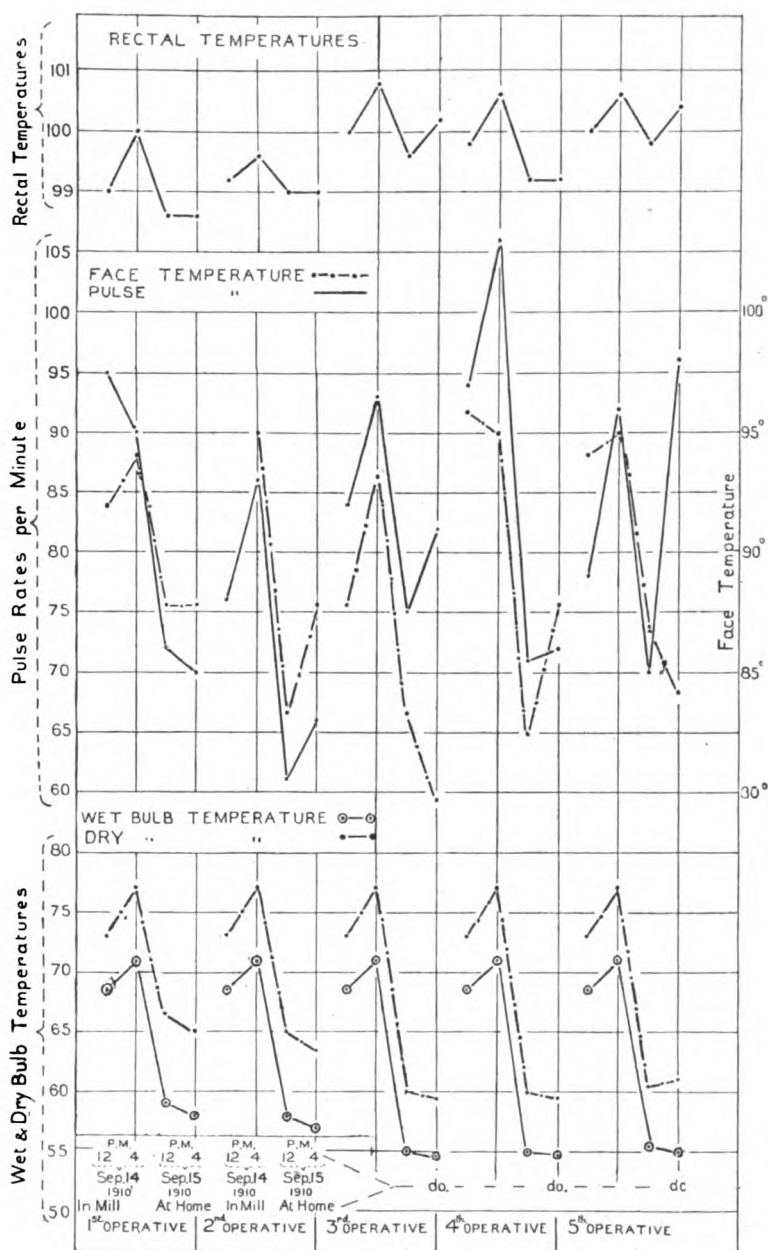


FIG. 1.

Effect of external temperature and moisture upon the pulse and deep and surface temperatures of the body.

the women, both trained and untrained, is related to age; the averages for the former group are 75.9 (under 25 years), 72.1 (25 to 30 years) and 70 (over 30 years); for the latter group 85.3, 83.4 and 78.1 respectively. In the case of the men the figures are—for the trained men, 71.5 (16 to 20 years), 64.1 (20 to 25 years), 61 (25 to 30 years) and 63.7 (over 30 years); for the untrained, 76.4, 75 and 70; and for the unfit, 82, 84 and 67 respectively.

The influence of temperature upon the rate of the pulse is shown in Fig. 1, which represents the results of observations

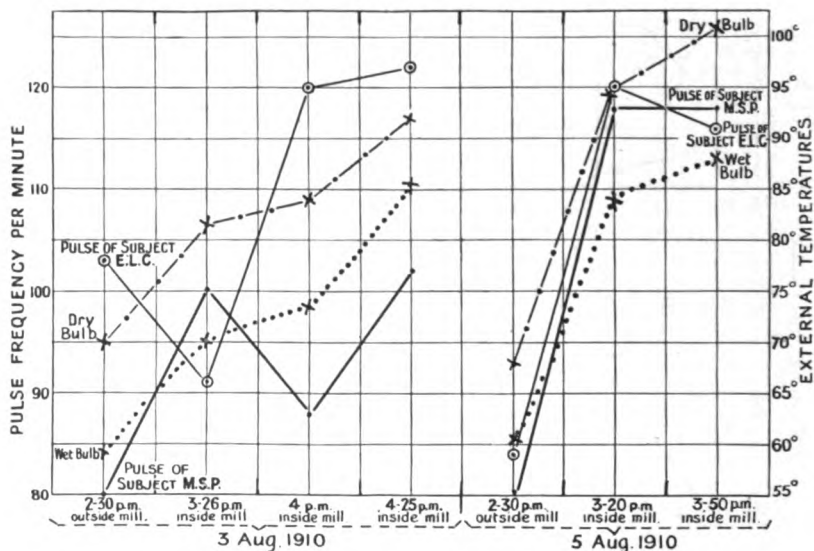


FIG. 2.

The effect of external temperature and moisture upon the rate of the pulse.

made by E. L. Collis and M. S. P. upon women operatives at a cotton mill. The curves for the rectal temperature, surface temperature of the skin of the face and temperature of the wet and dry bulbs closely resemble one another. Observations upon men operatives gave similar results.\*

The effect of the external temperature, as indicated by the readings of the wet- and dry-bulb thermometers, is shown by Fig. 2, representing the results of observations by E. L. Collis and M. S. P. upon themselves.\*

In each case a rise in the temperature of the air is followed by a rise of the pulse-rate at rest. There seems to be

\* Collis and Pembrey, Observations upon the effects of warm humid atmospheres in man. *Proc. Physiol. Soc., Journ. Physiol.*, 1911, XLIII., xi.



little doubt that the beating of the heart is quickened when the vessels of the skin are dilated, and there is no evidence that this increase is associated with a greater general metabolism. This becomes an important factor in relation to clothing during the performance of muscular work, as shown in Fig. 3.

The influence of time of day appears to be related to the activity and the temperature, both internal and cutaneous, of the subject and the temperature of the air, as shown by

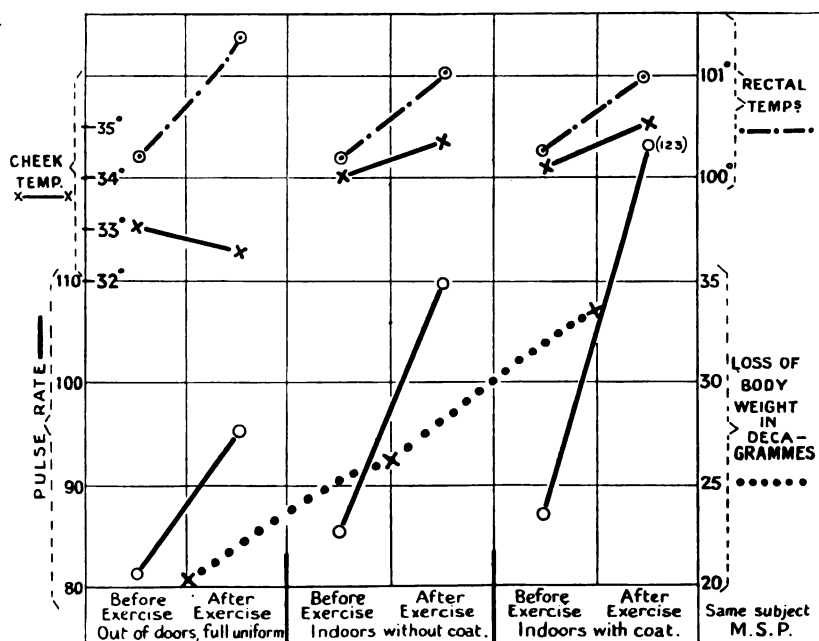


FIG. 3.

The average effects of similar amounts of exercise, but different clothing, upon the pulse, loss of moisture and deep and surface temperatures.

The average temperatures of the air by wet and dry bulbs respectively did not vary much during the series of 3, 5 and 9 experiments.

the wet and dry bulbs: the pulse tends to increase in rate with an increase in any of these factors (Table VI.).

We must consider now the *pulse as an indicator* of physical efficiency. In former papers results were given to show that the rate of the pulse after muscular work to which the subject is accustomed, is a good test of efficiency, for the reaction of the pulse to muscular exercise involves adequate adaptations of the nervous, respiratory, circulatory and muscular systems. There has been a tendency to take work upon a bicycle-ergometer as a standard. To such a form of exercise there are serious objections. It is not one to which the human race

TABLE VI.

VARIATIONS OF PULSE-RATE FROM MORNING TO AFTERNOON, FOR INDIVIDUALS AND GROUPS, SHOWN IN RELATION TO WET- AND DRY-BULB TEMPERATURES.

Subject.	Pulse.		Temperatures.		Rectal temperature.	Number of observations.	Times of day.
	Range.	Average.	Dry bulb.	Wet bulb.			
M. S. P.	74-90	81.0	71.2	60.3	99.6	5	10-11 a.m.
M. S. P.	80-96	85.9	69.4	58.6	100.2	18	2.30-3.30 p.m.
T. F. B.	68-70	69.0	64.4	52.5	100.1	4	10-11 a.m.
T. F. B.	66-82	75.0	68.4	57.6	99.7	6	3.30 p.m.
Averages for 7 men employed in a weaving shed. Observations by E. L. Collis and M. S. P.	71-103	92.4	72.1	67.6	99.6	7	10-12 a.m. Sept. 14, 1910
Do.	70-104	89.3	75.6	69.9	100.07	7	3-4 p.m. Sept. 14
Do.	64-95	78.6	60.0	55.4	99.7	7	10-12 a.m. Sept. 15
Do.	70-96	78.7	60.3	55.1	99.9	7	3-4 p.m. Sept. 15
Averages for 5 women employed in a weaving shed.	76-95	85.4	73.0	68.5	99.6	5	10-12 a.m. Sept. 14
Do.	86-106	93.4	77.0	71.0	100.3	5	3-4 p.m. Sept. 14
Do.	61-75	69.8	62.4	56.5	99.2	5	10-12 a.m. Sept. 15
Do.	66-96	77.2	61.7	55.8	99.5	5	3-4 p.m. Sept. 15

has been adapted, and there is a fixation of the thorax which affects adversely the respiratory and circulatory systems. In a tug-of-war these detrimental effects are frequently seen in collapse or fainting of members of the teams; the cause appears to be anoxæmia.

There is no doubt that walking and running are the exercises most readily and efficiently performed by man. In the previous paper the test exercise used was one of walking up and down a special staircase with steps of a particular height. As this is not a convenient test for general clinical purposes, we have substituted in the present experiments a stool thirteen inches high for the staircase, and reduced the duration of the test

from five to three minutes. The subject steps on and off the stool either 6, 12, 18, 24, 30, or 36 times per minute according to the respective exercise, the aim being to find two exercises, one of which produces a pulse ratio below 2.5, and another a ratio slightly above 2.5.

The exercises are plotted against the pulse ratios as shown in Fig. 4, and in this way it is possible, by joining the two points so found, to calculate the exercise necessary to produce a pulse ratio of 2.5. It was found for one subject, who was in extremely good training for football and boxing, that an exercise of 30 times a minute produced a pulse ratio of 2.24,

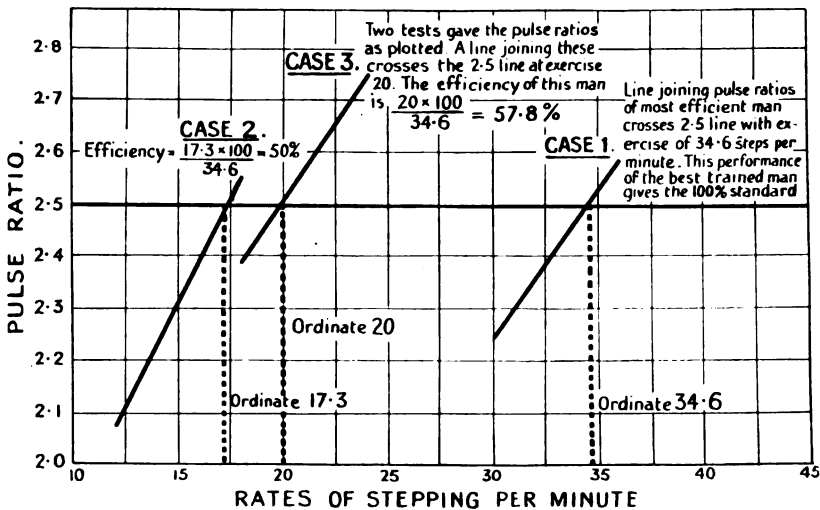


FIG. 4.

Diagram to illustrate the calculation of Efficiency from the Pulse Ratio.

and that an exercise of 36 times per minute resulted in a pulse ratio of 2.58. In the manner indicated it was possible to calculate that an exercise of 34.6 times per minute would produce a pulse ratio of 2.5. This man's efficiency was taken as 100, which served as a standard of comparison for the other subjects. Thus if a second man required an exercise of 17.3 ( $34.6 \div 2$ ) to produce a pulse ratio of 2.5, his efficiency was 50. If an exercise of 20 produced a pulse ratio of 2.5, the efficiency was  $\frac{20 \times 100}{34.6}$ , or 57.8.

In practice it is convenient in dealing with people apparently fit to start with an exercise of 18 times a minute, and to give a faster exercise if the ratio so produced falls below 2.5, and an easier exercise if it falls above 2.5. In pathological

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cases, such as well-compensated mitral stenosis without enlargement of the heart, the first exercise chosen should be 12 times per minute.

People who are accustomed to this test use their muscles to the best mechanical advantage, and practice, therefore, causes an improvement in their pulse ratio; for this reason it is advisable to let the subject step on and off the stool a few times before commencing the actual test. Stair climbing is natural to everyone, and therefore this form of test has a certain advantage over the stool test. But the stool test is on the whole more useful for clinical purposes, and it is easy for any physician to get a stool made of the required height, which he can use in his consulting-room.

Another convenient form of the "pulse ratio" test is one in which stepping on and off the stool is replaced by exercise up and down a flight of stairs. The heights, to which the body is raised by exercises of either 6, 12, 18, 24, or 30 times per minute, during three minutes' stepping on the thirteen-inch stool, are respectively 234, 468, 702, 936, and 1170 inches in a total of three minutes. The pulse ratio gives the same result if the work done in stair climbing is the same as that accomplished on the stool. In most houses the height of the stair is seven inches, and should such stairs be used for the test, the number of stairs to be climbed and descended in three minutes is either 33, 67, 100, 134, or 167. The only precaution to observe, in order that the results may be comparable, is that the ascent should be made at the same pace as the descent on a short flight of stairs, so that this exercise repeated 3, 6, 9, 12, or 15 times in three minutes on a flight of eleven stairs would involve practically the same work as the stepping test performed at 6, 12, 18, 24, or 30 times per minute for three minutes. The concordance of results of exercises on flights of stairs and on the stool is illustrated by the following records (Table VII.).

It will be seen from this table that the pulse ratio is the same whether the exercise be on the stool or on a flight of stairs, provided that the physical work done is the same. The only exception is with the ascent and descent of fourteen-inch stairs. The probable explanation is that the physiological work of descending the long steps face-forward is less than that involved in the other cases.

It is important to investigate whether the pulse ratio is of the same value for the extremes of resting pulse-rates. For this purpose the pulse ratio test was performed in the different temperatures of a Turkish bath.

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TABLE VII.

Subject, time, date.	Rate of exer- cise.	Laboratory.			1st Flight of Stairs.			2nd Flight of Stairs.		
		Pulse- rate before exer- cise.	Pulse- rate after exer- cise.	Pulse ratio.	Pulse- rate before exer- cise.	Pulse- rate after exer- cise.	Pulse- ratio after exer- cise.	Pulse- rate before exer- cise.	Pulse- rate after exer- cise.	Pulse ratio.
E. C. W. 10.30 a.m. 30.6.22	18	66	41 36 34 32 — 143	2.17	68	44 38 36 36 — 154	2.20	70	45 37 35 36 — 153	2.19
		Step 13" high. Exercise 18 times per min. for 3 min. $13" \times 18 \times 3 = 702"$ lift.			Step 5" high. Number of steps 14. 10 ascents in 3 min. $5" \times 14 \times 10 = 700"$ lift.			5 steps each 14" high, 1 step 7" high (flight 77") 9 times in 3 min. $77" \times 9 = 693"$ lift.		
E. C. W. 10.30 a.m. 28.6.22	24	71	58 41 35 40 — 174	2.45	66	90 71 — 161	2.44	—	—	—
		Step 13". Exercise 24 times per min. for 3 min. $13" \times 24 \times 3 = 936"$ lift.			Step 5" high. 14 steps. 13.5 ascents in 3 min. $5" \times 14 \times 13\frac{1}{2} = 945"$ lift.					
E. C. W. 10.30 a.m. 30.6.22	30	67	62 49 39 35 — 185	2.76	73	67 54 41 40 — 202	2.77	73	62 49 38 40 — 189	2.60
		Step 13". Exercise 30 times per min. for 3 min. $13" \times 30 \times 3 = 1170"$ lift.			Step 5" high. 14 steps. 17 ascents in 3 min. $5" \times 14 \times 17 = 1190"$ lift.			5 steps each 14" high and 1 step 7" high (flight 77") 15 times in 3 min. $77" \times 15 = 1155"$ lift.		
W. D. H. 10.30 a.m. 30.6.22	18	59	40 30 30 30 — 130	2.20	56	34 31 28 29 — 122	2.18	54	36 28 28 27 — 119	2.17
W. D. H. 10.30 a.m. 28.6.22	24	59	49 36 30 31 — 146	2.48	53	39 33 29 28 — 129	2.43	—	—	—
W. D. H. 10.30 a.m. 30.6.22	30	57	51 45 40 40 — 176	3.09	54	57 46 35 31 — 169	3.13	56	44 36 31 28 — 139	2.48
								56	49 34 30 29 — 142	2.54

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TABLE VIII.

Name.	Temperatures.		Pulse-rate before exercise.	Pulse-rate after exercise.	Pulse ratio.	Exercise steps per min.	Time.	Remarks.
	Wet bulb.	Dry bulb.						
W. D. H.	53	60	59	49 36 30 31 — 146	2.48	24	10.30 a.m.	Weight (net), 8 st. 3½ lb. In laboratory.
Do.	88	120	77	56 47 47 45 — 195	2.54	24	11 a.m.	Test taken after 7 min. seated in hot room.
Do.	95	142	92	130 123 — 253	2.75	24	11.45 a.m.	After 10 min. in this hot room. Final weight, 8 st. 1½ lb. Loss of weight=2½ lb.
E. C. W.	53	60	71	58 41 35 40 — 174	2.45	24	10.30 a.m.	Weight (net), 10 st. 1½ lb. In laboratory.
Do.	93	120	105	255	2.43	24	12 o'clock noon.	
Do.	95	142	139	? pulse too rapid for counting				Weight, 9 st. 13½ lb. Loss of weight=2 lb.

It will be seen that rises of pulse-rate of 18 (W. D. H.) and 34 (E. C. W.) had little effect on the ratio, but in the very hot atmosphere the ratio showed a higher value owing to the inefficiency produced by the heat.

The pulse ratio also gives similar values for the same person on consecutive days (Table IX.). Observations conducted at intervals on the same day on a subject, who had done no strenuous muscular exercises during the day, gave results closely agreeing with one another, although as the day progressed the pulse ratio became slightly higher, as shown by the table (Table IX.).

In preparing Table X. no special precautions were taken to avoid the complicating effects of previous strenuous muscular exercise, such as work in the gymnasium.

There remain to be considered several sources of fallacy.

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## TABLE IX.

VALUE OF PULSE RATIO ON DIFFERENT DAYS, AND AT DIFFERENT TIMES ON THE SAME DAY.

Subject.	Date.	Time.	Pulse-rate before test.	Pulse-rate after exercise in $\frac{1}{4}$ min. periods.	Pulse ratio.	Remarks.
W. D. H.	28.6.22	10.30 a.m.	59	146	2.48	Rate of exercise 24 steps per minute.
Do.	29.6.22	10.30 a.m.	59	49 36 30 31 —146	2.48	
Do.	30.6.22	11 a.m.	53	39 33 29 28 —129	2.43	
E. C. W.	17.6.22	7.45 a.m.	71	60 45 40 38 —183	2.58	
Do.	19.6.22	10.30 a.m.	73	56 40 —	2.47	
Do.	20.6.22	10.10 a.m.	66	84 } —180	2.53	Do.
Do.	27.6.22	10.50 a.m.	59	55 42 37 35 —169	2.53	
Do.	28.6.22	11 a.m.	66	48 38 31 32 —149	2.44	
Do.	29.6.22	10.30 a.m.	71	90 71 —161	2.45	
E. C. W.		10.30 a.m.	73	56 40 — } 84 } —180	2.47	
Do.	19.6.22	12.20 a.m.	65	51 44 34 34 —163	2.51	
Do.		3.45 p.m.	66	55 43 39 35 —172	2.56	
Do.		10.10 a.m.	66	55 42 37 35 —169	2.56	1 hour's strenuous tennis 8 to 9 p.m.
Do.		12.15 p.m.	64	50 — } 72 } 33 } —155	2.44	
Do.		3 p.m.	66	57 45 39 37 —178	2.69	
Do.	20.6.22	11 p.m.	87	58 47 44 43 —192	2.21	
Do.		11.20 p.m.	87	59 48 — } 88 } —195	2.24	

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TABLE X.  
PULSE RATIOS OF WOMEN TESTED FOUR TIMES IN ONE DAY.

Subject.	Time of day.	Resting pulse.	Pulse-rate for successive half-minutes.	Total.	Ratio.	Remarks.
A. Unfit.	9 a.m.-10 a.m.	86	—	213	2.48	Rate of exercise 18 steps per minute.
	12 o'clock-1 p.m.	66	59-44-40-39	172	2.60	
	2 p.m.-3 p.m.	66	58-45-40-40	183	2.77	
	4 p.m.-5 p.m.	66	61-48-41-42	192	2.90	
B.	As for A.	81	—	172	2.12	
		66	41-39-38-34	152	2.30	
		64	46-38-35-35	154	2.40	
		76	46-38-37-37	158	2.08	
C.	9 a.m.-10 a.m.	79	57-44-41-39	181	2.30	
	12 o'clock-1 p.m.	66	51-41-36-39	167	2.68	
	2 p.m.-3 p.m.	79	58-45-38-40	181	2.29	
C.	9 a.m.-10 a.m.	71	66-59-49-38	212	2.98	Rate of exercise 24 steps per minute.
	12 o'clock-1 p.m.	58	70-47-33-34	184	3.17	
	2 p.m.-3 p.m.	69	71-58-39-34	202	2.93	
	4 p.m.-5 p.m.	69	73-54-45-34	206	2.98	
D.	Do.	67	67-56-52-48	223	3.33	
		69	63-51-42-40	196	2.84	
		72	66-51-46-46	209	2.90	
		68	69-59-50-42	211	3.10	
E.	Do.	83	67-57-42-42	208	2.50	
		91	66-90-45	201	2.21	
		76	61-42-41-38	182	2.39	
		77	54-41-37-37	169	2.20	
F.	Do.	71	52-45-41-39	177	2.49	
		77	57-44-39-39	179	2.20	
		65	55-45-41-38	179	2.75	
		65	50-44-41-37	172	2.64	

It is well to do a small preliminary exercise on the steps for two reasons: the ratio improves with practice, and if, as the result of rest, the pulse had become somewhat sluggish, the ratio would be abnormally high. On the other hand, the subject should not have performed strenuous muscular work previous to the test, for, as the result of such work, the vascular system in a healthy person is in a better condition of tonus, and the slight exercise required for the pulse ratio test would be performed more economically and give a correspondingly low value (see Table IX.).

In order to test more thoroughly the influence of muscular work upon the pulse, observations were made upon medical students before and directly after a mile run—that is, after thirty-two laps round the longest room in the Physiological Laboratory. There were four turns at right angles in each lap, and these made the work more difficult and increased the time for the run, which as a rule was performed in eight minutes. The pulse was recorded graphically by an armlet connected with a recording tambour while the subject was sitting at rest; he then started to run the mile, and within ten seconds of its completion the pulse record was restarted and, apart



from definite pauses to prevent discomfort from venous congestion of the arm, was continued for about fifteen minutes.

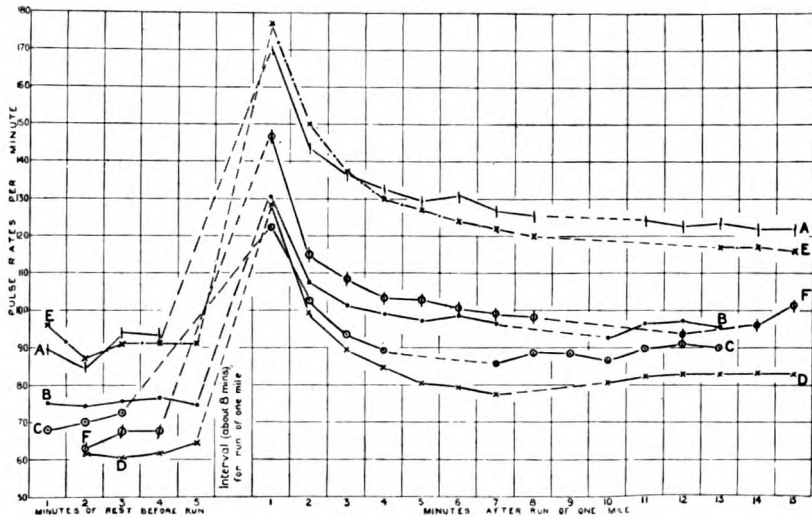


FIG. 5.

The rates of the pulse of six men before and after a run of 1 mile.  
For further details see Table XI.

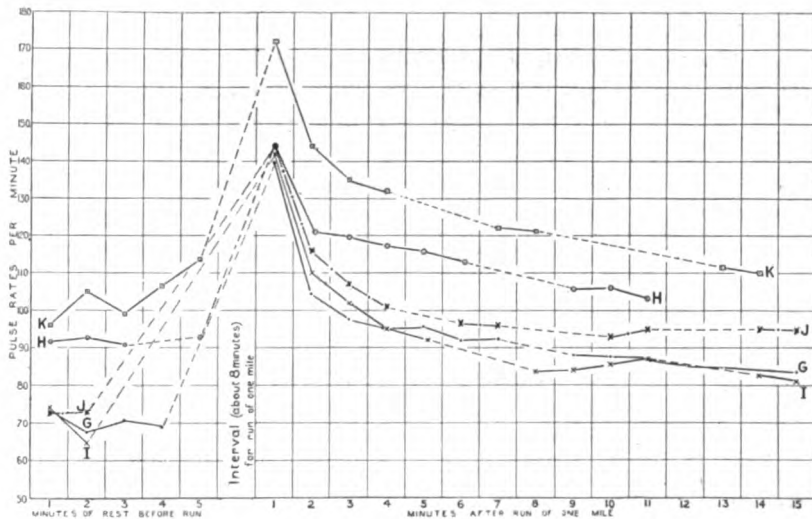


FIG. 6.

The rates of the pulse of five men before and after a run of 1 mile.  
For further details see Table XI.

The results of experiments upon eleven men are shown in the above curves (Figs. 5 and 6) and Table XI. The subjects

TABLE XI.  
PULSE RATES AT REST AND FOR 15 CONSECUTIVE MINUTES AFTER A RUN OF ONE MILE.

Subject and time for run.	Pulse seated.		Per cent. increase in pulse-rate immediately after run.	Actual pulse-rate after run.	Average Pulse-Rate in Minute Periods during 15 Minutes after Run.															
	Range.	Average.			1st min.	2nd min.	3rd min.	4th min.	5th min.	6th min.	7th min.	8th min.	9th min.	10th min.	11th min.	12th min.	13th min.	14th min.	15th min.	Pulse ratio.
A 7' 55"	84.5 to 94	90.2	126.2	204 11 secs. after	170	143.5	136.5 (47.2)	132.7	129.2	131	126.7 (40.4)	125.2	—	—	124.2	122.7 (36.0)	123.2 (36.5)	122	122	3.4
B 8' 10"	74.2 to 76.2	75.2	100.7	153 8 secs. after	130.7	107.7	101.5 (34.9)	99	97	98.7	96.2 (27.9)	—	—	92.7	96.5	97.0 (29.0)	95 (36.3)	—	—	3.2
C 7' 55"	68 to 72.5	70.2	122.2	156 15 secs. after	122.2	102.7	93.5 (33.2)	89.2	—	—	85.7 (22.2)	88.5	88.2	86.7	90.0	91.0 (29.6)	90.0 (28.2)	—	—	3.2
D 8'	60.2 to 64.5	62.6	149.2	156 15 secs. after	128.5	99.2	89.5 (43.0)	84.7	80.3	79.2	77.5 (23.8)	—	—	80.5	82.2	83 (32.6)	83 (32.6)	83.2	83	3.6
E* 8' 20"	87 to 96	91.2	110.4	192 9 secs. after	177	150	137.5 (50.7)	130	127	124	132 (33.7)	120	—	—	—	—	117 (28.2)	117 (28.2)	116	3.6
F 9'	63 to 67.7	66	154.5	168 15 secs. after	146.7	115	108.5 (64.4)	103.5	103	100.7	99 (50)	98	—	—	—	93.5 (41.6)	—	96 (45.5)	101.5	3.9
G 8' 35"	67.5 to 73	70	152.8	177	139.5	104.5	97.5 (39.2)	95	95.7	92	92.2 (31.8)	—	88	87.7	86.7	85.2 (21.8)	84.7 (21.1)	—	83.5	3.5
H† 7' 40"	90.7 to 92.7	91.9	76.3	162	144	121	119.5 (30.1)	117.0	115.5	112.8 (22.8)	—	—	105.7	106	103.2 (12.4)	—	—	—	—	2.9
I 8' 17"	64.8 to 74 only 2 min. record	69.4	142.1	168	142	110	102 (47)	95	92 (32.6)	—	—	83.5	84.0	85.5	87	—	—	82.5	81 (21.7)	3.6
J 9' 35"	72.5 to 72.6 2 min. record	72.5	115.1	156	144	116	107 (47.6)	101	—	96.5	96.0 (33.2)	—	—	93.0	95.0	—	—	95.0	94.8 (30.8)	3.6
K 9' 35"	96 to 113.4	104	84.6	192	172	144	135 (29.8)	132	—	—	122 (17.3)	121.2	—	—	—	—	111.5	111.0 (6.7)	—	3.0

\* Could only run 4 miles, attach.

† Could only run 12 miles.

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TABLE XII.

RESULTS OF PULSE RATIO TESTS.

Subjects A-K, who also performed running test (see Table XI).

Medical Student.	1st Test.				2nd Test.				3rd Test.				Efficiency expressed as a percentage (see text). Remarks.	Efficiency.
	Pulse before (1 min.)	Pulse after (2 min.)	Pulse ratio.	Steps per min.	Pulse before (1 min.)	Pulse after (2 min.)	Pulse ratio.	Steps per min.	Pulse before (1 min.)	Pulse after (2 min.)	Pulse ratio.	Steps per min.		
A	88	104 81 185	2.10	24	93	136 118 254	2.73	30	—	—	—	—	80%. Arrhythmia after stepping; no regular sport now; boxing Xmas 1921. Tonsillitis four times in period Oct./21 April/22.	80%
B	65	46 37 36 37 156	2.4	24	—	—	—	—	—	—	—	—	69%. Amateur weight-lifter, in training, practises weight-lifting three evenings a week. Biceps 13½ inches. Malaria 1920.	69%
C	54	44 35 29 30 138	2.56	24	—	—	—	—	—	—	—	—	In training. Day after test ran 100 and 220 yds. races hospital sports. Rugby twice a week in winter. At present plays match tennis.	69%
D	59	38 32 30 29 129	2.24	24	60	47 36 34 30 147	2.45	30	58	59 45 42 33 179	3.09	35	No sport now—fibrositis—otherwise fit. Plays in 1st XV.—arrhythmia after exercise but not at rest.	79%
E	74	99 100 199	2.55	18	78	107 94 201	2.58	18	—	—	—	—	Did not complete the mile run—much adipose tissue. Played Rugby football. One game cricket this season.	52%
F	65	51 38 36 35 160	2.46	24	67	53 40 37 34 164	2.45	24	—	—	—	—	Rugby football once a week in winter. High jump, tug-of-war, and putting weight at sports.	70%
G	72	55 44 40 37 176	2.4	30	73	69 66 48 44 217	2.97	36	—	—	—	—	Regular Rugby football player. International runner; now playing tennis and cricket.	88%
H	78	51 45 43 43 182	2.3	18	86	56 51 46 45 198	2.3	24	77	63 53 51 51 218	2.83	30	Did not finish mile run. Plays tennis every evening. Slight torticollis; heart and lungs healthy. Poor physical development.	76%
I	57	60 49 40 37 186	3.26	30	68	52 42 41 39 174	2.56	24	71	54 42 37 36 169	2.38	24	Long distance runner over 10 mile course. *Coughed several times.	71%
J	81	190	2.47	18	81	184	2.27	18	80	213	2.66	24	Some tennis now—no other sport—no illness.	55%
K	90	220	2.44	18	91	231	2.54	18	80	72 57 48 46 223	2.79	24	No sports; general breakdown in health a year ago.	52%

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were selected from the very fittest athletes, including an international runner, trained men belonging to the Rugby football team, men of average physique and training, and unfit men.

These results show definitely that the pulse ratio calculated from the data yielded by the run (Table XI.) does not agree with that given by the stepping test (Table XII.). The striking point is that the fittest men are those who showed as a result of the run the greatest percentage rise in pulse-rate. This confirms the value of the low resting pulse-rate of the athlete, for he has a greater range before the speed limit of the heart is reached. The extent to which the pulse-rate is above its resting value at the end of the fourteenth minute is no criterion as to fitness, but the extent of fall of the pulse from its highest value is a clear indication of fitness. This is shown by Table XIII.

TABLE XIII.

Subject.	Training.	Net weight in kilos.	Percentage increase of pulse-rate above resting value.	Per cent. above resting level at fifteenth minute.	Per cent. fall.	Remarks.
G. } D. } I. }	Best athletes	70 62 65	153 149 142	21 32 22	132 117 120	International runner. 1st XV. R.F. Cross-country runner.
F. } C. }	Very fit men	66 65	154 122	45 28	109 94	2nd XV. R.F. Good general athlete.
A. } B. }	Average men	58 58	126 101	36 26	90 75	Boxer. Weight lifter; high blood pressure.
J. } E. } H. } K. }	Unfit men	52 73 46 55	115 110 76 84	31 28 12 6	84 82 64 76	Tennis. Only did $\frac{7}{8}$ mile, stitch. Could do only 26 laps. General health poor.

The pulse ratio is valuable as a general test, but, as shown in the case of medical student H, it is not in every case a guide in an estimation of fitness for running the mile. The real test, as in everything, is the actual performance of the work required. In order to make the pulse ratio more reliable in such cases, it is advisable to count the pulse in half-minute periods, and thus obtain indications of the rate of recovery after the exercise. This precaution has been taken in all the later observations and the results indicate the value of the recovery of the pulse as a test for physical fitness (Table XIV.).

TABLE XIV.

AVERAGE EXCESS ABOVE RESTING VALUE OF PULSE-RATE IN FOURTH HALF-MINUTE  
AFTER STEPPING TEST.

(24 steps per minute for 3 minutes.)

Best athletes.		Very fit men.		Average men.		Unfit men.	
Average.	Range.	Average.	Range.	Average.	Range.	Average.	Range.
0.5	1.5 to — 1.0	0.95	4.5 to — 1.5	2.1	5.0 to — 1.5	8.1	13 to 3

*Results*

The average rate of the pulse at rest in 406 observations on 94 men is 74.7 with a range from 52 to 106; of 103 observations on 103 women 79.5 with a range from 53 to 116.

The largest individual range of the pulse rate at rest among 18 men is 36; among 18 women 57.

In healthy subjects the rate of the pulse at rest varies according to weight and surface area of the body, age, physical training, deep and surface temperatures of the body, and temperature and moisture of the air.

The pulse-ratio, that is the ratio between the pulse rate for the two minutes immediately following the given *mild* muscular exercise and the pulse rate at rest, is a good indicator of the physical fitness of the subject.

The pulse ratio taken after *running a mile* is no indicator of fitness. The fittest men are those who showed the greatest percentage rise in the pulse rate, and the greatest percentage fall towards the resting value.

We wish to express our thanks to Sister Angove, Misses Higham, Frances, Prosser, Smith and Clarke of the Department of Remedial Exercises, Guy's Hospital; Miss E. L. M. Surie of Chelsea Physical Training College, Miss H. W. Bainbridge, and the numerous students who have given their help in the observations.

## CHRONIC APPENDICITIS AND APPENDICULAR DYSPEPSIA

By ARTHUR F. HURST, M.D., Physician to Guy's Hospital.

“WE cannot doubt that, as advancing knowledge brings us better means of investigation, and so enables us to discover and distinguish structural changes, of which we now can only observe the functional results, the aggregate of maladies called dyspepsia must undergo successive subtraction, tending more or less completely to its total subdivision into special maladies.” (Brinton, 1844.)

The first suggestion that chronic inflammation of the appendix may cause dyspeptic symptoms appears to have been made as long ago as 1896 by Rutherford Morison.<sup>1</sup> Three years later Ewald<sup>2</sup> drew attention in Germany to the same subject in an article on “appendicitis larvata.” But it was not until 1910, when Moynihan<sup>3</sup> introduced the term “appendix dyspepsia,” that the frequency of the condition became widely recognised in England and in America, where a paper on the subject was published about the same time by Graham and Guthrie<sup>4</sup> from the Mayo Clinic.

The importance of chronic appendicitis as a cause of gastric symptoms is now firmly established. But it is interesting to recall the reception which Moynihan's original article met with on its appearance in the *British Medical Journal* in January 1910. Sir Anthony Bowlby<sup>5</sup> complained of the vagueness of the clinical picture which had been drawn, and predicted that “one result of Mr. Moynihan's paper will be that many ‘dyspeptic’ people will undergo operations for the removal of the appendix, and the great majority of them will be none the better.” Contrast this with the question asked by Sir Clifford Allbutt<sup>6</sup> the following week in reference to the same article: “May we not ask ourselves if there is not something in it—perhaps a great deal—immature, fragmentary if you please, yet with a core of important truth?” The twelve years which have since elapsed have shown the wisdom of both writers. Few will now deny that there is “a great deal in it,” that Sir Berkeley Moynihan's paper contained such a valuable “core of important

truth " that it may be regarded as almost epoch-making. But every physician and surgeon of experience must agree that Sir Anthony Bowlby's fears were to some extent justified, and that numerous dyspeptic people—though certainly not "the large majority"—who have had their appendix removed for supposed appendix dyspepsia, have been none the better for it. My chief object in writing this paper is to draw attention once again to the great value of the x-rays and of Bastedo's inflation test in the diagnosis of chronic appendicitis for appendix dyspepsia. I would indeed go so far as to say that no operation should be performed for this condition until the diagnosis has been confirmed by these means. If this practice became the rule, it would, I believe, be very rare for an appendix to be removed unnecessarily.

#### SYMPTOMS

The gastric symptoms which may result from chronic appendicitis are probably caused by the reflex stimulation of the motor and secretory nerves of the stomach. The vomiting of acute appendicitis is obviously reflex in origin, and I shall presently describe how an ocular demonstration of the appendicular-gastric motor reflex can sometimes be obtained with the x-rays in chronic cases. The gastric hypersecretion, which Bonar has shown occurs in 88 per cent. of cases of chronic appendicitis with gastric symptoms, is doubtless of similar reflex origin (*vide* p. 400). The sensory symptoms probably result from the combined effect of these motor and secretory disturbances on the activity of the stomach.

Chronic appendicitis may give rise to gastric symptoms, which are either the sole manifestation of the disease, or are accompanied by constant discomfort or short attacks of pain in the right iliac fossa. Epigastric pain, which may radiate downwards to the umbilicus or below, and occasionally towards the right iliac fossa, occurs after meals. The time of its onset is very irregular. Most commonly it occurs immediately after meals, but occasionally it is delayed for two or three hours. It is at the most only slightly relieved by alkalies, and food very rarely gives even momentary relief. It is aggravated by exercise to a greater extent than is the case with the pain of gastric and duodenal ulcer. The degree of discomfort varies from time to time; it is rarely completely absent, and may sometimes be sufficiently severe to compel the patient to stay in bed. Nausea is common and is often present in the absence of vomiting. It is sometimes produced by pressure on the abdomen, especially over the appendix, and it may also follow exercise. Vomiting may occur, especially immediately or soon after food and when

the pain is severe, but it gives much less relief than in gastric ulcer. Heartburn and acid regurgitation are uncommon.

Hæmatemesis is often said to be a symptom of appendicular dyspepsia. The truth is that the appendix, like the teeth and tonsils, may act as a focus of infection which may give rise to acute ulcers of the stomach or duodenum. These appear to give rise to no symptoms in the majority of cases, but erosion of a blood vessel may occur and cause hæmatemesis, and in rare cases such an ulcer may perforate. Most frequently the hæmatemesis is neither preceded nor accompanied by gastric symptoms. If, however, they do occur, they are not due to the acute ulcer, but to reflex appendicular dyspepsia; or they may be due to accidental association with nervous dyspepsia or with the dyspepsia which is such a common symptom in chlorotic girls, independently of their possible association with chronic appendicitis or acute gastric ulcer, or both. Under certain conditions the acute ulcers, which result from infection in the appendix or elsewhere, may become chronic, but much more often they heal rapidly, owing to the absence of the essential predisposing conditions which constitute the "ulcer diathesis," in the absence of which a chronic ulcer cannot develop.

Tenderness is generally more marked in the right iliac fossa than in the epigastrium, even when there is no spontaneous pain in the former situation. Occasionally the localised tenderness can only be discovered when pressure is exerted directly over the appendix after it has been rendered visible with the x-rays. In many cases pressure in the right iliac fossa leads to no local pain, but to discomfort in the epigastrium which is sometimes accompanied by nausea, exactly simulating the spontaneous symptoms.

Constipation is commonly present. In rare cases there may be chronic diarrhœa, but more frequently a form of pseudo-diarrhœa occurs, in which frequent small stools are passed owing to the irritation of the rectum caused by a chronically inflamed appendix situated in the pelvis. Pelvic appendicitis may also lead to irritability of the bladder with frequent micturition, and to dysmenorrhœa in women.

#### X-RAYS IN THE DIAGNOSIS OF APPENDICITIS

The radiography of the appendix is a comparatively new field of investigation. Bécère<sup>7</sup> in 1906 appears to have been the first to obtain a radiogram of the appendix. In 1911 Grigorieff<sup>8</sup> stated to a congress of physicians in Moscow that the appendix becomes filled with opaque material in all cases



in which its lumen is in full communication with that of the cæcum. In 1913 George and Gerber<sup>9</sup> claimed that the appendix could be seen in 70 per cent. of their patients, and in the following year<sup>10</sup> I drew attention for the first time in England to the great value of the x-rays in the diagnosis of disease of the appendix. Since then numerous important contributions to the subject have been published, amongst which may be mentioned those of Spriggs<sup>11</sup> in 1919 and Redding<sup>12</sup> in 1921.

In my opinion no operation for chronic appendicitis is justifiable unless the diagnosis has been confirmed by means of the x-rays. The x-ray evidence is both direct and indirect; the former concerns the examination of the appendix itself, and the latter is concerned with the effect of chronic appendicitis on the rest of the alimentary canal. The sign of greatest importance is the direct determination of appendicular tenderness (*vide infra* (1) (c)); this by itself is sufficient to enable a definite diagnosis to be made in a large majority of cases.

(1) DIRECT EVIDENCE.

(a) *The Shadow of the Appendix.*—The appendix is

much more frequently visible in normal individuals than has generally been supposed, if proper means are taken to look for it.

The examination should be made between six and twenty-four hours after the barium meal. A small diaphragm is used, and the cæcum and ileum are pushed from side to side in an attempt to move them out of the way of the appendix, if the latter is not seen without doing this. In some cases the patient should turn gradually on to his left side so as to obtain lateral views in case the appendix is situated behind the cæcum. It can be seen more or less clearly in at least 80 per cent. of normal individuals. It is visible with equal frequency in chronic appendicitis, when its shape and size, and the rate of filling and emptying can be investigated. More important is the discovery of its position in relation to the cæcum and terminal ileum, and the position of the cæcum in the abdomen. This often throws light on cases in which anoma-

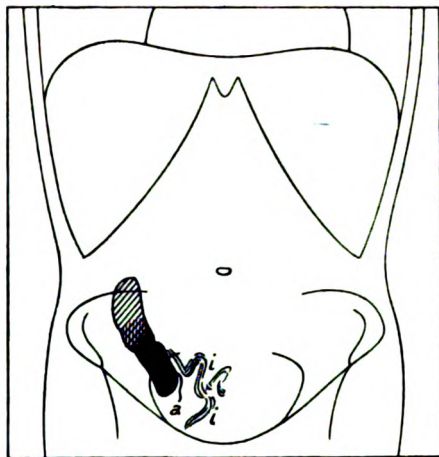


FIG. 1.

Tracing of terminal ileum, *i*, cæcum, ascending colon, and appendix, *a*, in case of pelvic appendicitis.

lous symptoms have resulted from the appendix being situated in the pelvis (Fig. 1), behind the cæcum, unusually high—when the symptoms may simulate those of gall-stones or duodenal ulcer, or even on the left side.

There is no diagnostic significance in the absence of an obvious shadow of the appendix. On the other hand, I have seen the appendix quite clearly in a patient who had had an appendicular abscess opened abroad; she did not know whether the appendix had been removed, and its discovery with x-rays made it justifiable to advise operation for recurrent pain in the right iliac fossa. In a second case the x-ray examination showed that the appendix was still present and very tender, although the patient's parents had been clearly given to understand by an Austrian surgeon that he had removed it during an acute attack fourteen years earlier. Its subsequent removal by Mr. Warren Low was followed by permanent relief from abdominal attacks which had become increasingly frequent during the last seven years. In another case an inflamed appendix had been removed from a patient suffering from severe rheumatoid arthritis; the latter rapidly disappeared after the operation, but some months later the symptoms gradually returned. An x-ray examination showed that the stump of the appendix was still present, and that barium remained in it at least seventy-two hours longer than in the cæcum. As the stump was exceedingly tender, and was also the only fixed point of the whole bowel, a further operation was clearly indicated.

(b) *Adhesions in the Right Iliac Fossa.*—The presence of adhesions in connection with the appendix, terminal ileum, and cæcum, whether to each other or to the surrounding parts, can be recognised by deep palpation during a screen examination. Great care is required to avoid diagnosing adhesions by this method of examination when they are not present, but adhesions of any importance are not likely to be missed. If the cæcum is in the pelvis it can often be drawn into the right iliac fossa by manipulation under the screen. When this cannot be done, it is impossible to determine whether adhesions are present, as the cæcum and appendix are too deep to be palpated satisfactorily, unless the colon is distended with air or the bladder is not emptied for ten or twelve hours before the examination. If the appendix is adherent to the pelvic wall or to a pelvic organ other than the bladder, it does not rise under these circumstances. Sometimes the ileum appears to be fixed where it crosses the pelvic brim; but by manipulation the whole loop can be raised out of the pelvis and the apparent adhesions and kink disappear. On one occasion (Fig. 2) I saw what looked

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like a typical ileal kink, the ileum being fixed where it passed over the brim of the pelvis; no amount of manipulation had any effect upon it, but on inflating the bowel in carrying out Bastedo's inflation test for appendicitis, the distended pelvic colon lifted the last part of the ileum completely out of the pelvis, and palpation now showed that there were no adhesions and no

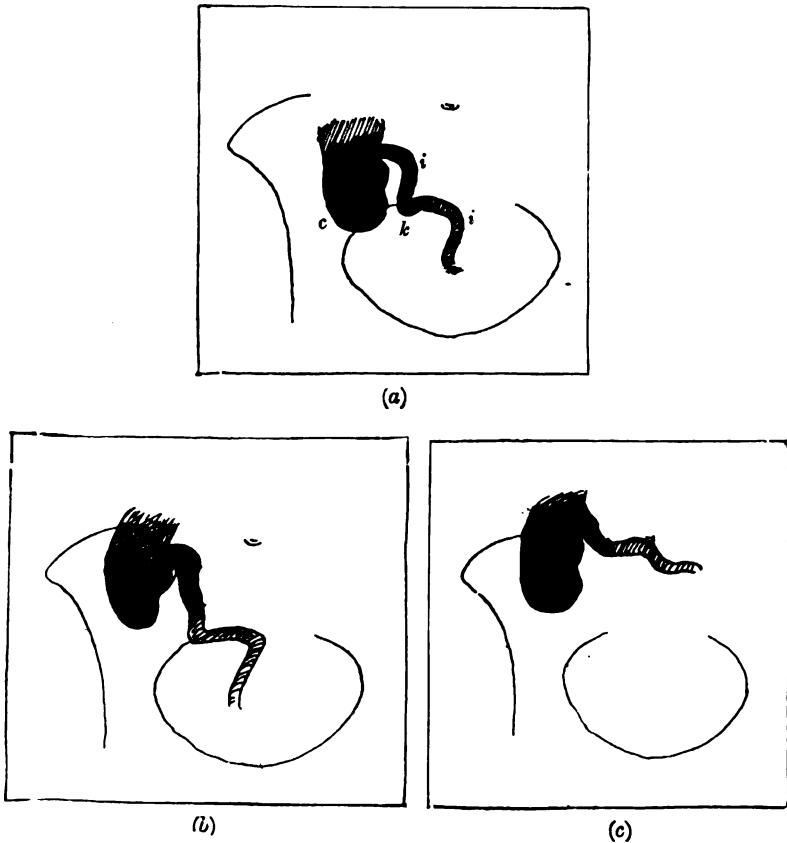


FIG. 2.

(a) Apparent ileal kink (*k*) at brim of pelvis; *c*, caecum; *ii*, end of ileum. (b) Caecum raised by pressure of fingers; "kink" still present. (c) Disappearance of "kink" after inflation of the colon.

kinks. Before a diagnosis of an ileal kink can be made with the x-rays the colon should therefore be inflated, if palpation has failed to separate the apparent adhesion.

(c) *Tenderness of the Appendix.*—The x-rays have demonstrated that in chronic appendicitis tenderness is confined to the whole or more frequently to some part of the appendix itself, the part apparently corresponding to an inflamed area or to the position of one or more concretions. When the caecum and

appendix are pushed aside by one hand, pressure upon the appendix with the other shows that it is still the maximum point of tenderness, whilst pressure over the original point of tenderness now causes no pain; this proves that true visceral tenderness and not referred tenderness is being demonstrated. If typhlitis is also present, as in infections with the *Entamæba histolytica*, the cæcum may be tender in addition, and in rare cases the ileum, if firmly bound down by adhesions, may be also tender. But if the appendix is the primary source of the disease, it generally remains the most tender point.

On ordinary examination of the right iliac fossa the parts are unavoidably displaced when pressure is exerted; it may happen that the appendix itself thus escapes direct pressure. I have found on several occasions that the appendix, when palpated under the screen, was exceedingly tender, although no tenderness had been observed immediately before on pressing in the right iliac fossa without the guidance of the x-rays.

In most instances the appendix is quite impalpable, and it would therefore be impossible without the x-rays to be certain whether the appendix itself was the seat of the local tenderness. Even when it is not filled with barium, and is therefore not visible with the x-rays, local tenderness in a situation, which from its relation to the cæcum and termination of the ileum is likely to be that of the appendix, is strong evidence in favour of appendicitis.

(d) *Concretions and Foreign Bodies*.—The right iliac fossa should always be examined with the x-rays before the barium meal is taken, as in rare cases a concretion, and still less frequently a foreign body can be seen in the appendix. Spriggs has pointed out that in many cases the barium passes round a soft concretion, which then gives the appearance of a vacuole.

(2) INDIRECT EVIDENCE. (a) *The Stomach: Hypertonus; Spasmodic Hour-glass Contraction; Reversed Peristalsis*.—Chronic appendicitis may be associated with a hypertonic condition of the stomach, which empties itself with abnormal rapidity. This is much less frequently observed than with duodenal ulcer, and the extreme degree often seen in the latter condition is very rarely present in appendicitis. More commonly a spasm occurs in the centre of the stomach. Indeed, chronic appendicitis is, after gastric ulcer, the most common cause of spasmodic hour-glass constriction of the stomach. In an earlier issue of the "Reports" the diagnosis of this condition from organic and orthostatic stricture was discussed (p. 168). I have on a few occasions seen a spasm develop in the middle of the stomach when pressure was exerted over the appendix, and Mr. P. Briggs

has seen the normal peristalsis become suddenly much more active under the same conditions; in most cases epigastric discomfort was simultaneously produced, occasionally without any accompanying pain in the right iliac fossa. I have twice seen reversed peristalsis in the stomach associated with chronic appendicitis, although there was no trace of pyloric obstruction, and the stomach emptied itself at the normal rate. These are the only exceptions I have met with to the rule that reversed peristalsis is pathognomonic of pyloric obstruction. It should be noted that the reversed peristalsis was less regular than that generally seen in pyloric obstruction. Feeble waves occasionally passed backwards from a point about three inches from the pylorus on the greater curvature at the same time as normal peristaltic waves started from the same point on their way to

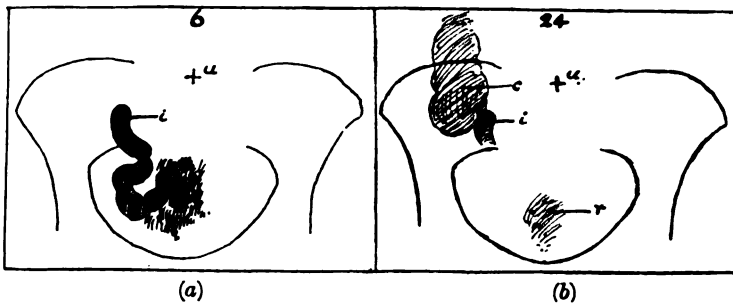


FIG. 3.

Ileal stasis due to reflex closure of the ileo-cæcal sphincter in chronic appendicitis. *i*, terminal ileum; *c*, cæcum; *r*, rectum; *u*, umbilicus.

the pylorus. There was no delay in the evacuation of the stomach and at the operation nothing abnormal was seen in either the stomach or duodenum. In one case the appendix was associated with an undescended cæcum and was therefore very near the pylorus; this fact may have been responsible for the abnormal gastric peristalsis.

(b) *Ileal Stasis*.—The normal stasis which occurs in the end of the ileum is increased in all conditions which lead to spasm or to inhibition of the normal relaxation (achalasia) of the ileo-cæcal sphincter. The most important of these conditions is appendicitis. In the case of a middle-aged gentleman with symptoms of chronic appendicitis the stomach was empty six hours after the bismuth meal, but no bismuth was present in the cæcum, all of it having collected in the end of the ileum, though in the average normal individual the shadow by this time should have reached the hepatic flexure (Fig. 3). The last few inches of the ileum could be clearly defined, as they were distended

with chyme. Palpation under the screen showed that there were no adhesions, the whole of the ileum being freely movable. Twenty-four hours later some bismuth was still present in the last inch and a half of the ileum and a little in the cæcum and ascending colon, all the rest having passed to the rectum, from which some bismuth-containing fæces had just been evacuated. It was clear, therefore, that the only stasis in this patient's alimentary canal was in the end of the ileum. Mr. R. P. Rowlands operated and removed an inflamed appendix full of pus, but found that the ileum was perfectly normal and was free from adhesions. The ileo-cæcal junction was not abnormally narrow, so that it was clear that the stasis could have been due to nothing else than achalasia or spasm of the ileo-cæcal sphincter.

(c) *Cæcal Stasis*.—Chronic appendicitis frequently causes stasis in the cæcum and ascending colon by giving rise to reflex inhibition of the normal mass peristalsis. In such cases the x-rays show that the cæcum and ascending colon are often abnormally large and unusually mobile.

The greater part of the opaque meal remains in the cæcum and ascending colon at the end of twenty-four hours and often after forty-eight or even seventy-two hours. The barium may pass through the rest of the colon at the normal rate, so that after twenty-four hours, a small quantity may be seen in the neighbourhood of the splenic flexure or even in the pelvic colon, from which it may be expelled in the stool, although the greater part has not yet passed the hepatic flexure.

In one such case the appendix, cæcum, and ascending colon were full twenty-four hours after the meal, and some barium was seen in the rectum, but otherwise the colon was empty. The cæcum was freely movable and could be drawn without difficulty from the pelvis, in which it was situated, both on lying down and standing. The tip of the appendix, however, remained adherent to the pelvic brim, its junction with the cæcum being exceedingly tender.

(d) *Rectal Stasis or Dyschezia*.—When the appendix hangs over the brim of the pelvis, or when the cæcum as well as the appendix is situated in the pelvis, chronic appendicitis may give rise to dyschezia. In one such case (Fig. 4) the rectum (*r*) was already distended with barium-containing fæces ten hours after the meal, though no desire to defæcate was felt; the cæcum was still full, but the other parts of the colon were nearly empty. The appendix (*a*), which was clearly visible with the x-rays, was in close relationship with the rectum and was very tender on pressure; it showed obvious signs of chronic inflammation when removed.

(e) *Enterospasm*.—Chronic appendicitis is the most common of the reflex causes of enterospasm. The x-rays generally show that the lumen of the colon is abnormally narrow in various short portions of its length, the exact position changing from one examination to another. The part most commonly affected is the proximal half of the transverse colon, and the contracted segment is generally shorter than what is observed in other forms of enterospasm. The constipation present in these cases is the result of interference with the normal peristalsis of the

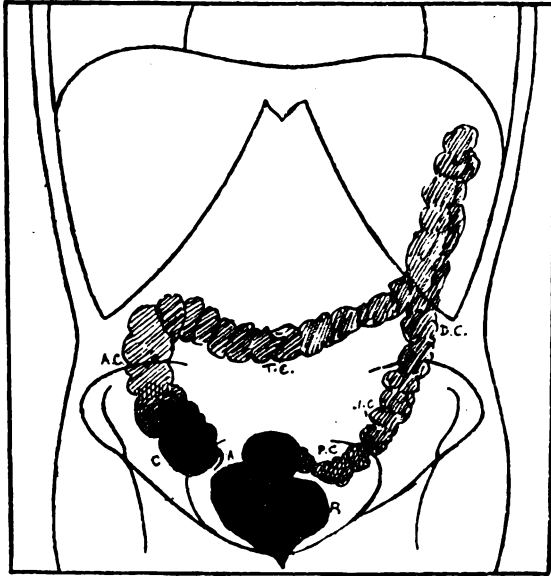


FIG. 4.

Chronic appendicitis giving rise to dyschezia. Tracing taken ten hours after a barium meal, showing rectum (R) distended with fæces, though no desire to defæcate was felt. The appendix (A), which was very tender to pressure and showed obvious signs of chronic inflammation when removed, is in close relationship to the rectum. The cæcum (C) is full, but the other parts of the colon (A.C., T.C., D.C., I.C., P.C.) contain only a little barium.

colon and is not due to the mechanical obstruction offered by the contracted intestine, as the x-rays show that no delay occurs in the passage through the contracted segment, and that there is no dilatation of the bowel immediately proximal to it.

#### BASTEDO'S SIGN

In a paper published in 1909 Bastedo<sup>13</sup> of New York described a sign which he believes is of great value in the diagnosis of chronic appendicitis. In 1913 I published a paper<sup>14</sup> entirely confirming his observations. The test is simple to

carry out, causes very little inconvenience to the patient, and is, in my experience, more reliable than any sign hitherto described, with the exception of the discovery with the x-rays of tenderness localised to the appendix.

The test depends upon the production of pain and tenderness in the right iliac fossa on inflation of the colon with air. For this purpose I use an ordinary rubber rectal flatus tube, which is connected with the nozzle of a Higginson's enema syringe. Bastedo recommended that the tube should be inserted eleven or twelve inches into the rectum, but, as a tube can very rarely be passed beyond the pelvi-rectal flexure, which is situated four and a half inches from the anus, there is no advantage in introducing it further than just within the ampulla of the rectum—about an inch and a half from the anus. After the tube has been inserted the patient lies flat on his back, and the pump is brought up between his legs. On now slowly pumping air through the tube the colon is seen gradually to distend, and after a certain quantity has been introduced an individual who is not suffering from appendicitis feels a diffuse discomfort in the lower part of the abdomen, but there is no pain unless an excessive quantity of air is introduced, in which case it is not more marked on one side than the other. There is also no tenderness. Patients suffering from appendicitis, however, generally experience pain in the right iliac fossa, even if the pain has hitherto been confined to the epigastrium or the neighbourhood of the umbilicus. In one of my cases, in which a diseased appendix was subsequently removed, pain was only felt some hours later. Whenever pain is produced, and in some cases in which no pain has been felt, well-marked tenderness is found in the right iliac fossa. When tenderness has already been observed in this situation, it is generally much increased by inflation, but it is also found in cases in which no tenderness has hitherto been noticed in spite of frequent examinations. In a number of instances I have observed a further exceedingly characteristic sign; the pain is referred to the epigastrium when pressure is exerted in the right iliac fossa after inflation, the epigastric pain being identical in character with that which formed the chief symptom of which the patient complained. Occasionally no pain was felt in the right iliac fossa on inflation, but the patient complained of epigastric discomfort and sometimes nausea, identical in character with the symptoms which occurred spontaneously.

The test known as Rovsing's sign, although it had been employed by Dr. Lauriston E. Shaw for some years before Rovsing's first publication on the subject, in which pain is felt in



the right iliac fossa on exerting pressure over the descending colon, has a similar significance to Bastedo's sign, as it appears to depend upon gas being pressed from the distal into the proximal part of the colon. It is, however, of limited use, as it is comparatively rare for sufficient gas to be present in the descending colon. After the colon has been inflated in the carrying out of Bastedo's test, and the pain produced has disappeared, it can often be caused to return by pressing upwards along the descending colon, as in Rovsing's test.

In my own experience I have only obtained a positive Bastedo's sign in appendicitis, the appendix having always been found diseased at the subsequent operation, except in a few cases in which inflation of the colon gave rise to pain in the right iliac fossa, although the appendix had previously been removed. In such cases adhesions were probably present. In one such case Rost found a band passing from the side of the cæcum, which was otherwise abnormally movable; in all probably the pain resulted from the pull of this band upon the distended and movable cæcum when the colon was inflated. In most cases in which the abdomen has subsequently been explored in spite of a negative Bastedo's sign, the appendix has been found to be healthy; in some cases disease has been discovered in the female pelvic organs, the gall-bladder, or the right kidney or ureter.

A negative response to the test does not definitely exclude appendicitis, but the probability of its presence is small in that case, and very clear evidence of other kinds is required before an operation for the removal of the appendix could be justified.

In my Goulstonian Lectures<sup>15</sup> I showed that the only stimulus to visceral pain is distension. On inflating the colon the pain eventually produced occurs no sooner in the appendix than in the rest of the colon, so long as the former is not diseased, but if it is inflamed, pain and tenderness are observed in the right iliac fossa. It is not yet clear to what extent adhesions binding down the appendix may be concerned in the production of the pain, but in some of my cases there were no adhesions, so that the chief factor in Bastedo's test is probably distension of the diseased appendix.

#### TREATMENT AND THE QUESTION OF FOCAL INFECTION IN CHRONIC APPENDICITIS

Complete recovery should follow the removal of the appendix for chronic appendicitis, but it is not infrequent for the symptoms to persist for a time after the operation, especially in anæmic, neurasthenic or hysterical patients. It is best

in such individuals to give a preliminary course of treatment before the operation is performed in order to improve their general condition, and it is important that the patient should have a sufficiently long rest afterwards instead of being allowed to get up in the usual way—often before the end of a fortnight.

Infected teeth and tonsils are so common that their association with appendicitis might be regarded as accidental, were it not for the recent remarkable investigations carried out by Rosenow.<sup>16</sup> He has shown that intravenous injection of streptococci and much less frequently of *B. coli* isolated from a diseased appendix into rabbits produces appendicitis. He has also shown that streptococci isolated from the teeth, the apices of which are infected, and from infected tonsils in cases of appendicitis, show a selective action on the appendix when inoculated into rabbits, appendicitis being produced in 68 per cent. of the animals, just as streptococci from the teeth and tonsils in cases of gastric or duodenal ulcer and in cholecystitis show a selective action on the stomach or duodenum (60 per cent.) and the gall-bladder (80 per cent.) respectively. On the other hand, streptococci isolated from infected teeth or tonsils in the absence of disease of the appendix, stomach and duodenum, or gall-bladder, rarely cause appendicitis (3 per cent.), gastric and duodenal ulcer (17 per cent.), or cholecystitis (4 per cent.).

Rosenow has shown that the streptococci isolated from the appendix, teeth or tonsils in cases of appendicitis have no effect when introduced into the lumen of the normal appendix, in spite of their specific action on the appendix when injected intravenously. Only when chronic inflammation has resulted in damage to the mucous membrane or to stasis in the appendix owing to the presence of fæcoliths, strictures or kinks from adhesions, is further infection from the lumen of the bowel likely to take place. Swallowed streptococci originating in pyorrhœa alveolaris and tonsillitis may then lead to secondary infection and recrudescence of inflammation which is latent or has died completely out, especially if the oral sepsis is associated with achlorhydria, which deprives the stomach of the normal antiseptic action of the gastric juice. Under the same conditions pathogenic strains of *B. coli* or streptococci in cases of colitis involving the cæcum may also lead to secondary appendicitis.

In spite of their specific affinity for the appendix the streptococci isolated in cases of appendicitis are culturally almost identical with those obtained in other diseases, and they soon lose their specific action on passage through animals. The not uncommon association of appendicitis with gastric ulcer and

especially with duodenal ulcer, and also with cholecystitis, suggests that the streptococci may have a specific affinity for more than one organ or may in course of time vary in their specific affinities.

From these considerations it is clear that removal of the appendix in cases of chronic appendicitis may not lead to the complete disappearance of the patient's symptoms. The teeth should be x-rayed in order that any apical infection, which may occur in the complete absence of pyorrhœa alveolaris, may be discovered, and every septic focus in the teeth, tonsils and nasal sinuses should be eradicated—if possible before the abdominal operation is undertaken. In this way many of the disappointments due to the coincidence of colitis and early or latent cholecystitis, and to the recurrence of hæmatemesis from acute gastric or duodenal ulcers should be avoided; with the possible exception of the cholecystitis no local surgical treatment carried out at the same time as the appendicectomy is likely to be of any use.

In slight and doubtful cases, in which an immediate operation is obviously unnecessary, no harm can be done by waiting to see whether the removal of foci of infection, together with the administration of dilute hydrochloric acid in adequate doses if achlorhydria is present, does not lead to complete and permanent recovery. I do not, of course, suggest any such delay if a definite attack of acute or subacute appendicitis has occurred, or in long-standing cases of unmistakable chronic appendicitis, but every surgeon will welcome the possibility of avoiding the necessity of operating on the doubtful cases, which so often are incompletely cured or whose state of invalidism may even be exaggerated by operation.

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## THE GASTRIC SECRETION IN APPENDICITIS AND CHOLELITHIASIS

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### I. APPENDICITIS

CHRONIC appendicitis may manifest itself either in symptoms localised to the right iliac fossa or in symptoms which are mainly gastric, the latter group being commonly known as appendicular dyspepsia. Whereas the symptoms in the former group are due to attacks of subacute inflammation developing on the top of chronic appendicitis, and depend directly upon the actual pathological processes occurring in the right iliac fossa, the symptoms in the latter are undoubtedly reflex in origin. Evidence of their reflex origin has been obtained by a study of the motor functions of the stomach in these cases (*vide* p. 392). The investigations described in this paper have been carried out with the object of ascertaining whether similar reflex secretory abnormalities occur.

All the cases were examined by means of a fractional test-meal, and the results obtained show a striking difference in the two types of cases I have just described. In forty cases the symptoms were confined to the right iliac fossa. Of these, twenty-two (55 per cent.) showed achlorhydria or hypochlorhydria; six (15 per cent.) showed normal acidity, and twelve (30 per cent.) showed high acidity. In twenty-five cases of appendix dyspepsia none showed achlorhydria or hypochlorhydria; three (12 per cent.) showed a normal curve, and twenty-two (88 per cent.) showed hyperacidity, thirteen of the latter having a characteristic pyloric or duodenal type of curve.

These percentages should be compared with those obtained by Bennett and Ryle in one hundred normal students, four of whom showed achlorhydria and ten hyperchlorhydria. The excessive number of cases with achlorhydria or hypochlorhydria in the first group of cases is in striking contrast with the absence of achlorhydria from the second group with appendix dyspepsia. The most probable explanation is that the achlorhydria is a predisposing cause of chronic appendicitis rather than a result

of the condition, as the absence of free hydrochloric acid from the stomach must render it abnormally easy for infection of the bowel and appendix to occur. On the other hand, the hyperchlorhydria found in the second group of cases is probably a reflex result of the chronic irritation of the appendix, and is responsible with the reflex motor disturbances in the stomach for the gastric symptoms, which are not observed in the other cases.

## II. GALL-BLADDER

Thirty-five cases of gallstones have been investigated. Of these seventeen (49 per cent.) showed achlorhydria, ten (29 per cent.) had a normal curve, and eight (23 per cent.) had hyperchlorhydria. The very large proportion of cases with achlorhydria is probably due to the absence of gastric juice predisposing to duodenal infection and consequent ascending infection of the bile-ducts, the achlorhydria being, as in the first group of appendix cases, a predisposing cause and not a result of the disease. The proportion showing hyperchlorhydria, though much smaller, is a good deal greater than in normal individuals and is probably, like the hyperchlorhydria of appendix dyspepsia, reflex in origin. It has, however, not been possible to divide the gallstone cases into two groups according to their symptoms corresponding to the two groups described in the case of appendicitis.

## STUDIES ON TUMOUR FORMATION

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### IV. ACQUIRED TISSUE MALFORMATIONS

THE malformations that have been discussed in the preceding studies are congenital, or at least depend upon disturbances that have taken place during the development of the organs of the body. There are others that have originated after the development of the tissues was completed. They are of no little interest and importance to us, since we often know the causes that are responsible for their production. Again, they are similar to and comparable with the ante-natal malformations, and help us to understand the ætiology of many of these.

I have pointed out that congenital tissue malformations merge imperceptibly with certain tumours, the so-called hamartomata. This is equally true of those that owe their being to the accidents of adult life.

Post-natal or, to be accurate, post-developmental malformations can be subdivided into anomalies of bulk and of differentiation, and into those of position and of blending. This classification enables us to compare them with those whose origin is developmental.

1. *The Hypoplasias*.—I need do no more than mention the hypoplasias and atrophies. Because of deficient blood-supply, impairment of function, the fibrosis of healed inflammatory lesions, more or less obscure conditions known as degenerations, and other disturbances of metabolism, certain changes are set up in a part. Its cells are diminished in number, in size, and in the height of their differentiation. The most highly organised cells, namely the epithelia, are those that suffer first and most severely, whereas the connective tissue stroma usually proliferates. The conversion of liver cells into so-called bile-capillaries, and the new formation of the latter that frequently accompanies the atrophy of the secreting epithelium, can be taken as a type of these changes. Compare Fig. 33, which represents a nodule of sub-capsular atrophy of the liver, with the congenital anomaly depicted in Fig. 13 (II.). Essentially they are both of them substitutions of highly organised secreting

epithelium by less highly differentiated conducting epithelium, accompanied by overgrowth of connective tissue. Whether the substitution be a direct conversion of liver cells, or a replacement by proliferated bile-capillaries, it is difficult to say. But there can be no doubt that it is induced by the stimulation to regenerative activity coincident with, and very probably dependent on impairment of function. Since the regenerative proliferation is slight, the loss of differentiation is not great. But it is present, and corresponds closely with the appearances seen in many of the congenital tissue malformations that have been discussed in Study II.

2. *The Hyperplasias.*—The possible relationship of the

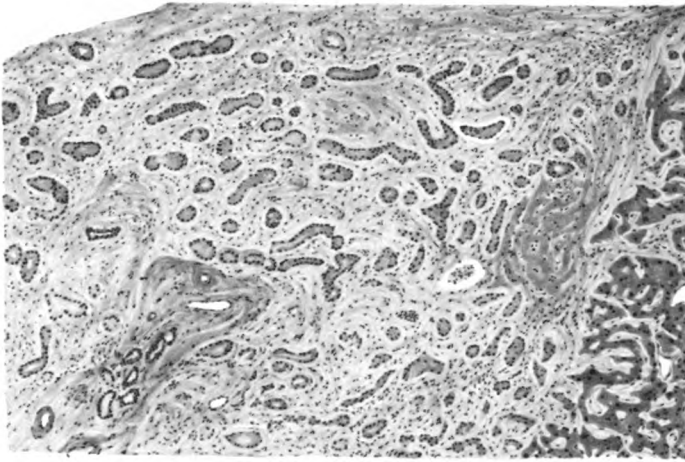


FIG. 33.

Localised sub-capsular atrophy of liver. Magnif., 80.

hyperplasias to blastomatous proliferation will have to be discussed later. A few structural peculiarities may, however, be considered here.

A hyperplasia is often localised. It then forms a nodule which, on account of its isolation, frequently resembles a tumour so closely that it becomes impossible to decide upon its true status. Such hyperplasias are typical hamartomata. They occur with great frequency in certain cases of cirrhosis and sub-acute atrophy of the liver. The large, soft, rounded, bile-stained nodules which often replace a great part of the organ in these conditions are well known to every one. Their resemblance to tumours is accentuated by their failure to unite with the bile ducts and by the consequent accumulation of

secretion. I have seen such a nodule in an otherwise healthy liver. It was well defined to the naked eye, but the microscope showed that it passed gradually into the surrounding tissue. Near its centre its cells were large, and their nuclei were increased in number and in size. But these differences gradually disappeared as the periphery was reached. It is, of course, open to any one to say that this nodule had originated in an error of development. Such a statement, however, cannot apply to the multiple nodules in cirrhotic livers. These are clearly attempts at compensating the antecedent destruction of epithelium. Since cause and effect are obvious, they are

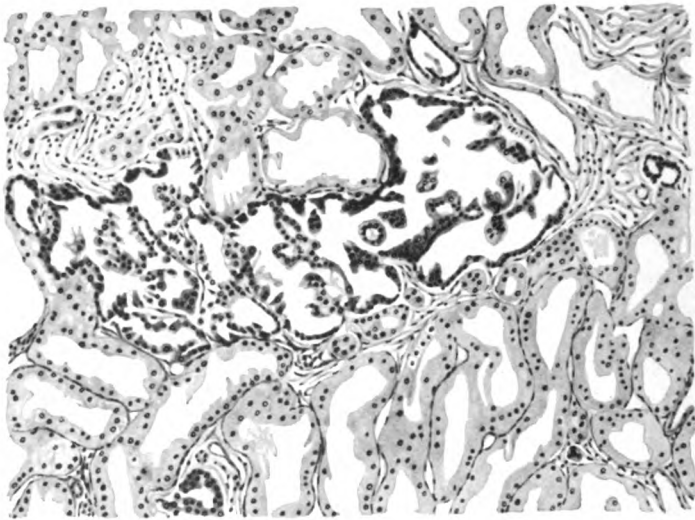


FIG. 34.  
Hyperplasia of tubules of granular kidney. Magnif., 110.

always classed among the compensatory hyperplasias. It is only when, as in the case of an isolated nodule in an otherwise healthy organ, its ætiology is obscure, that we are tempted to fall back upon a congenital anomaly and to relegate it to the tumours.

This argument applies with equal force to the so-called adenomata of granular kidneys. Fig. 34 represents an early stage of one of these. We see an irregular tubular formation, which is split up into inter-communicating lumina by extremely delicate connective tissue septa and papillæ, lined by one or more layers of small, deeply stained epithelial cells with relatively large nuclei. Three isolated lumina, lined by identical epithelium, are to be seen in the drawing. Two of these probably



communicated with the first at other levels, whereas the third did not. Similar tubules were found in other parts of the organ. I have seen them on many occasions, and have traced all stages from small simple lumina to large "adenomatous" formations. I have satisfied myself that many of the latter are enormously distended renal tubules, sub-divided by ingrowths of connective tissue covered by proliferating epithelium, which after a time assumes an independent, blastomatous mode of growth. I was able, on one occasion,<sup>6</sup> to demonstrate a connection between the lumen of one of them and a renal tubule. The epithelial proliferation is an attempt at compensatory hyperplasia. It is of common occurrence in granular kidneys, and I have never seen it in a healthy organ. Buds grow outwards from

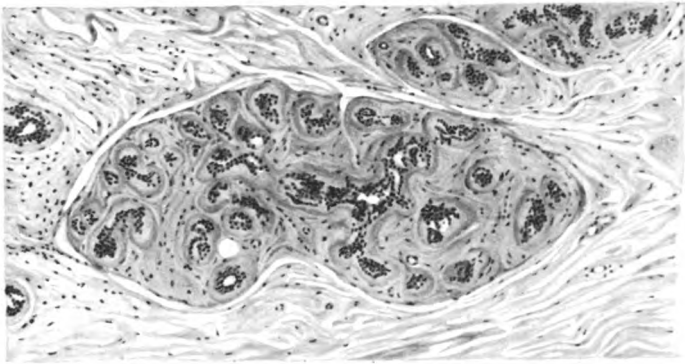


FIG. 35.

Chronic mastitis. Mammary lobules resembling fibro-adenomata. Magnif., 90.

the hypertrophied tubule. It sometimes attains a large size and becomes encapsulated, and acquires all the characters that we associate with an adenoma. Malignant tumours of the kidneys are found, whose structure is identical. These will be referred to again later.

Hyperplasia of the stroma of an organ produces an isolation of its epithelium, which is often suggestive of a congenital malformation. If the epithelium has not been destroyed or its growth inhibited by the fibrosis, it can itself proliferate and take on an atypical structure, and give rise to a genuine hamartoma. It is difficult to judge the extent to which isolation is responsible for this atypical proliferation, and that to which it is produced by the irritation consequent on a mild form of inflammation, or some metabolic disturbance of a more general nature.

Figs. 35 and 36 illustrate this. They were drawn from cases of chronic mastitis. The former represents two mammary lobules, together with part of a third, the intra-lobular stroma of which had proliferated and become sclerosed, producing a striking resemblance to a fibro-adenoma *en miniature*. These appearances were not localised, but were found in all parts of the breast. Unless we are prepared to believe that practically every lobule of this organ had been malformed since birth, and that the general fibrosis has had nothing to do with the changes, we are forced to admit that a lesion acquired through the accidents of life can and does bear a remarkably close and



FIG. 36.

Chronic mastitis. Mammary lobule resembling intra-canalicular fibro-adenoma. Magnif., 85.

highly suggestive resemblance to a fibro-adenoma or mixed tumour.

Fig. 36 represents a somewhat different condition. Numerous cysts are seen at the edges of the drawing. They are the remains of dilated mammary acini, surrounded and separated from each other by a diffuse fibrosis of the intra- and inter-lobular connective tissue of the breast. The centre of the figure is occupied by a lobule, whose stroma has proliferated and given rise to a loose, œdematous, "myxomatous" granulation tissue, which has compressed and elongated the secreting tubules. Their epithelium has proliferated to the extent of keeping pace with their elongation, if it has not actually exceeded it. This area, which is quite unencapsulated, and whose loose stroma extends between the bundles of fibrous tissue at its periphery, bears an unmistakable resemblance to an intra-canalicular

fibro-adenoma mammæ. It was the only one of its kind found in this breast. I have, however, seen multiple lobules, whose structure is identical, in the compressed and fibrotic mammary tissue at the periphery of a large encapsulated fibro-adenoma. The changes become less marked as we pass outwards from the tumour, and the altered lobules gradually merge with normal tissue at the edges of the compressed area. Even if we are inclined to assume that the solitary structure in Fig. 36 is a congenital malformation, such an assumption is impossible in the second case.

Albrecht's<sup>1</sup> definition of a hamartoma is that it is a tumour-like malformation. Its essential characteristic is an abnormal mixture of the normal constituents of the organ in which it is found. The anomaly can be one of quantity, arrangement, differentiation, or of two or all of these factors. It arises in an abnormal mixture of tissues, or in a disturbance of their differentiation. Albrecht believed that nearly all the hamartomata owe their existence to a disturbance during development, and that their anlage is nearly always congenital, even when they do not make their appearance until late in life. He, however, admitted the possibility that some hamartomata are formed in the fully developed adult organism. He included the fibro-epithelial tumours of the breast (the peri- and intra-canalicular fibromata, as he named them) in this group of tumour-like malformations. I have tried to show, in the first of these studies, that these new growths bear a close, if a distorted, resemblance to the mammary gland. The structures depicted in Figs. 35 and 36 differ from them in no essential detail. Were they some hundreds of times as large as they are, they would be passed over without comment as a fibro-adenoma and an intra-canalicular fibro-adenoma by every one. I regard them as early stages of these tumours, as the "germ" or "cell-rest," in the sense of Cohnheim's theory, out of which a hamartoma can grow. They are, therefore, themselves hamartomata. There is no valid reason whatever why an unbiassed observer should consider them to be congenital malformations; all the evidence shows that the changes of chronic mastitis are responsible for their presence. They are malformations acquired in adult life. I therefore propose to extend the name of "malformation" to these and to similar post-developmental anomalies. To limit the definition to a structure whose origin can be proved to have been due to an error of development\* is, in my opinion, a mere juggling with words, if it can be

\* It is often not as easy to furnish this proof as the writings of many pathologists would lead us to suppose.

shown that others, with identical characters, arise in the fully developed body.

I conclude, therefore, that some fibro-epithelial tumours or hamartomata of the breast owe their existence to a post-developmental malformation which has, in turn, resulted from the effects of an inflammatory or other pathological lesion. I am prepared to extend this conclusion to adenomata of the kidney (*vide* Fig. 34) and to similar hamartomata.

Far be it from me to wish to generalise, or to attempt to prove that all hamartomata and adenomata are acquired in adult life. On the contrary, it is my object to show that a dual origin is possible, and that they occasionally arise in cells and tissues whose developmental history has been perfectly normal.\*

The next phenomenon I wish to draw attention to here is one that is frequently met with in chronic ulcerations and superficial inflammations. It consists of an increase of the physiological tendency of every lining epithelium to cover naked granulations and tissue spaces that do not already possess an endo- or epithelial covering. The epithelium lost on the surface of an ulcer is replaced by proliferation of the cells that have survived at its edges. If the base of the ulcer is smooth, the epithelium covers it in a single sheet. If, however, it is occupied by granulations, these acquire a covering of their own, which dips downwards between them, branches and anastomoses where they are in contact, and often extends for a considerable distance beneath the surface. Appearances not unlike those of a carcinoma are produced, and some little experience is required if a wrong diagnosis is to be avoided. Thus, the proliferation of the cells of the epidermis in tuberculous lesions of the skin and mucous membranes is sometimes very similar to a squamous or columnar celled carcinoma. In the former condition it does not extend deeper than the granulation tissue, and never shows signs of infiltration, nor does it invade the lymph channels that possess an endothelial lining.

Fig. 37 represents the appearances seen in a case of chronic suppuration of the lachrymal duct of the lower eyelid in a boy of thirteen. The upper part of the drawing corresponds with the wall of the duct, its lower part is the edge of a large mass of granulations that distended its lumen. Healing had begun in the superficial part of the duct, where (in the left half of the figure) its fibrous wall is covered by a thin layer of granulations with wide capillaries. They are lined by a partly macerated

\* I claim no more than was done at one time (see the introductory paragraphs to Study II.) by Ribbert.<sup>9</sup>

squamous epithelium, which dips between them as shallow irregular papillæ. In the deeper parts of the specimen, where the inflammation was more recent and active, the wall is covered by thick, branched, œdematous granulations. Every one of these possesses an epithelial covering, which is branched in accordance with its contours, and often appears to be isolated in the section. The epithelium does not, however, reach the deep surface of the granulations. Those that occlude the lumen of the duct possess a similar covering of squamous epithelium.

I do not know if the presence of squamous epithelium in the lachrymal duct, whose normal lining is said to consist of a

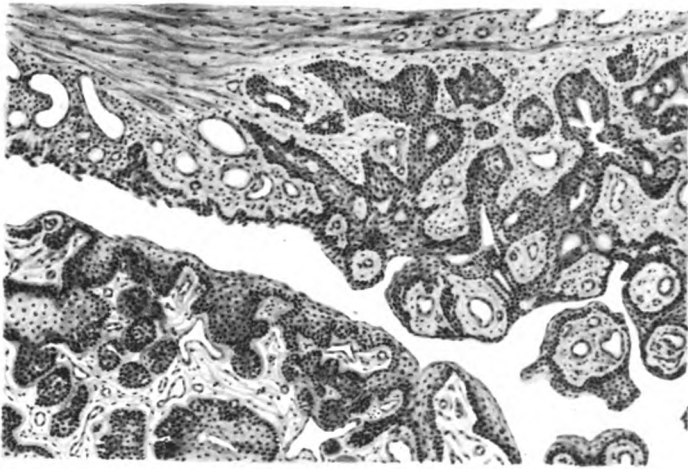


FIG. 37.

Lachrymal duct. Extension of epithelium between granulations. Magnif., 90.

ciliated respiratory mucous membrane, be due to replacement of the latter by the epidermis of the eyelid, or to an alteration of its differentiation (*vide infra*) induced by the pathological environment. Nor does this matter very much, since the specimen clearly shows that the squamous epithelium, once it has arrived, forms a complete lining to all the granulations. When these are absorbed as healing advances, its deep processes disappear likewise. The specimen illustrates a hyperplasia of the physiological function of squamous epithelium to cover raw surfaces, which depends solely upon the presence of granulations in need of a covering.

It is possible, of course, that small pieces of epithelium might not have become absorbed during the process of healing,

had this not been surgically interfered with. They would then have persisted as minute epidermoid cysts.

The tendency of epithelial cells to form a covering to raw surfaces sometimes leads to remarkable results. Meyer<sup>5</sup> has described an inflammatory stricture of the sigmoid colon, the sinuses of which were lined by intestinal epithelium. Its cells had extended through the wall of the gut, and had followed the blood vessels into the root of the mesentery and into a lymph-gland. Their spread was continuous in the tissue spaces loosened by inflammation. They did not enter the lymphatics, although the latter were invaginated by columns and tubules of epithelium. Meyer points out that the epithelium has assumed no malignant characters in this case.

3. *The Heteromorphoses (Heteroplasias).*—In a recent paper<sup>7</sup> I have collected a number of anomalies of position. They consist of normal cells joined to form perfectly normal tissues, but found in unusual situations. Some of them are congenital, or at least developmental, and due to abnormal differentiation of the cells of the organ in which they are found. The term "heteroplasia" is best restricted to these. They have been briefly discussed in the second of these studies. Others arise in originally normal tissues in a number of pathological states, most of which are associated with irritation and inflammation of a more or less chronic kind. These are the prosoplasias and metaplasias of epithelium, and the heterotopic differentiations of connective tissue.

A *prosoplasia* is characterised by a degree of differentiation in excess of that normal for the organ. Thus, the transitional epithelium of the urinary passages is a squamous epithelium, which consists of only a few layers of cells, in which fibrillation is not, as a rule, apparent, and without traces of prickle-cells, of keratohyalin, or of keratinisation. After long-continued irritation, however, its differentiation can advance to the production of a typical thick rete Malpighii with papillæ and prickle-cells, a stratum granulosum, and a stratum corneum, with keratohyalin and copious keratinisation.

When an epithelium undergoes *metaplasia* its cell characters become altered. For example, the columnar epithelium of the cervix uteri is converted into squamous epithelium. This metamorphosis, which is infinitely more frequent in the simple conducting than in the more highly organised secreting epithelia, is an atypical regeneration in response to an abnormal environment, since it requires a more or less intense and long-continued proliferation to induce it, and is found, apart from new growths, in chronic inflammatory lesions.

The best known of the *heterotopic differentiations* of connective tissue is the formation of bone in calcified necrotic foci. These act like irritating foreign bodies and become surrounded by granulation tissue, which absorbs the lime salts. The local supersaturation with these stimulates the lowly organised young fibroblasts to become differentiated into bone corpuscles and to deposit a bony matrix, instead of undergoing differentiation into connective tissue corpuscles.

I need not here discuss these conditions again fully. They teach us the very important lesson that the normal degree and direction of differentiation of the cells of the body depends upon their site and environment, as well as upon their intrinsic capabilities. If the environment becomes pathological, the cells even of the fully developed adult body react to it by alterations of the extent (prosoplasia) or the direction (metaplasia) of their differentiation. An anomaly, corresponding in every respect with a so-called error of development, arises in fully differentiated tissues.

The extent to which the conversion of one kind of epithelial cell into another can take place is strictly limited and, in the adult body at all events, does not go beyond that of columnar into squamous epithelium and, more rarely, *vice versa*. Even in the developmental heteroplasias it is confined within the potentialities of the germinal layer and of the organic system to which a tissue belongs.\*

I now come to a specimen which appears to occupy a position intermediate between a simple hyperplasia and a prosoplasia. Fig. 38 represents a part of an undescended testis of a boy of ten. The seminal tubules present an immature appearance which corresponds with the age of the child. At the centre of the figure there is a large tubule, which has been cut across twice. It is in a state of active spermatogenesis. To its left there is a group of interstitial cells. This tubule is the only one of its kind seen in the sections. Its cells have undergone a degree of differentiation very much in excess of that to be expected at the corresponding age, and especially in an undescended organ. It represents a disturbance of tissue equilibrium of Ribbert,<sup>9</sup> such as this author believed to be liable to excessive and blastomatous proliferation, and to form the starting-point of a malignant new growth. In the

\* I have been met with the objection that, if heteromorphoses occur, there is no reason why the liver should not give rise to ganglion cells. I can only answer that there is no reason at all that I can see why it should not, except the unanswerable one that it does not do so. I have collected certain facts in my paper, and have attempted nothing more than to give them a reasonable explanation.

present instance it has undergone a hyper-differentiation, a change in the opposite direction. This tubule would, I presume, have been the last of all those in the testis to give rise to a neoplasm, since differentiation and boundless proliferation are incompatible with each other.

4. *Traumatic Epidermoid Cysts*.—When a piece of epidermis is driven into the body by means of a blunt-pointed instrument, it occasionally becomes established in the subcutaneous tissue, and survives more or less indefinitely. Its cells proliferate and become differentiated in the same manner and at approximately the same rate as they would have done had it remained



FIG. 38.

Undescended testis of boy of ten. Tubule with active spermatogenesis. Magnif., 115.

on the surface. The germinal cells of the rete Malpighii constantly produce prickly-cells, which eventually undergo keratinisation. At a very early stage after implantation a small mass of dead horny cells is formed on the side of the graft opposite to its germinal layer. It acts as an irritant to the fibroblasts that come into contact with its free surface. They form a layer of granulation tissue over it, which always contains a number of foreign-body giant cells, whose business it is to ingest and to remove the insoluble flakes of horn. A cavity or epidermoid cyst, as it is called, is produced. It is filled with horny flakes and debris, and is only partly lined by epithelium. The raw granulations that are in contact with the rest of its circumference stimulate the epithelium to cover



them, and its germinal cells therefore spread along the surface. They, however, constantly undergo physiological differentiation and give rise to more dead horny flakes. These accumulate, and cause an enlargement of the cavity which keeps pace with the efforts of the epithelium to surround it. A vicious circle is set up, and the epithelial lining never becomes complete. This is well shown in Fig. 39, a section through a large traumatic epidermoid of the pulp of the finger. It agrees in this respect



FIG. 39.

Traumatic epidermoid of pulp of finger, filled with desquamated horny flakes. Its epithelial lining is incomplete, its circumference partly surrounded by granulation tissue. Semi-diagrammatic. Rete mucosum black. Stratum lucidum of epidermis light grey. Stratum corneum dark grey. Magnif., 5·3.

with the complicated ovarian dermoids or teratomata, whose origin is, of course, congenital.

These epidermoids illustrate the fact that cells that have been displaced do not remain dormant or tend to excessive growth. Proliferation and differentiation go hand in hand, and remain within strictly physiological limits.

5. *Abnormal Blending of Epithelia*.—The accessory suprenals in Figs. 24 and 25 (III.) illustrate the fact that, when two kinds of epithelium come into immediate contact with each other, the cells of each proliferate and invade those of

the other. The suprarenal cells have grown more vigorously than those of the kidney, many of whose tubules have been completely surrounded by them (Fig. 24). Since these cases are developmental anomalies, due to displacement of suprarenal cortex, it might be argued that the greater amount of proliferation exhibited by the epithelium of the suprarenal is due to the fact that it has been displaced at an early period of embryonic life, and that its cells have therefore acquired a degree of independence and power to grow at the expense of others, which is greater than that of normally placed tissues.

Fig. 40 shows that this is not true. Here the liver was cirrhotic and Glisson's capsule thickened and inflamed. The

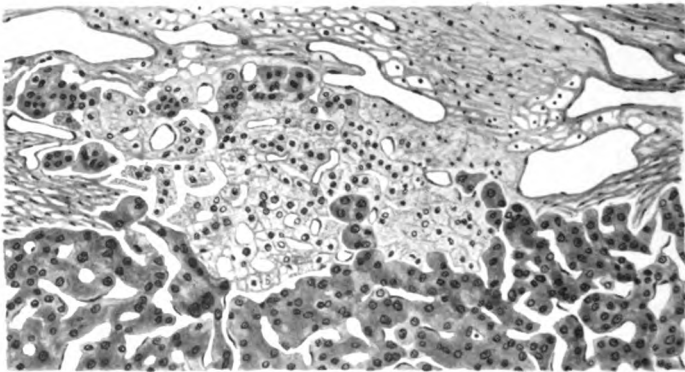


FIG. 40.

Adhesion of suprarenal to cirrhotic liver. Defect of Glisson's capsule. Infiltration of each other by the two epithelia. Magnif., 180.

fibrosis had extended to the capsule of the right suprarenal, where it lies on the surface of the liver, and had produced an abnormally firm union of these organs. At one spot Glisson's capsule was defective, and the yellow suprarenal could here be seen with the naked eye to extend for a short distance into the brown hepatic tissue. Fig. 40 represents a part of this area. Here the suprarenal cells extend into the liver, with whose epithelium they are in immediate contact. But the latter has sent three prolongations between them, all of which project to, and even slightly beyond, the level of Glisson's capsule, showing that they must have resulted from an active growth of hepatic cells. These appearances are strictly comparable with those in Fig. 25 (III.), and prove that the power to invade strange epithelia is shared by the cells of the suprarenal, liver and kidney.

A very similar case has been recorded by Oberndorfer.<sup>8</sup> In a syphilitic child of fifteen months the right suprarenal was firmly attached to the cirrhotic liver by means of a greatly thickened capsule, from which fibrous septa extended into its substance. Atrophic suprarenal cells were found in the capsule, and between it and the parenchyma of the liver. He believes that groups of suprarenal cells were displaced by the traction exerted by the newly-formed fibrous tissue, and that they were gradually pressed into the liver, where they were absorbed. In Schmorl's<sup>10</sup> case the right suprarenal was found under the capsule of the liver. It was invaded by bile-ducts and trabeculae of hepatic cells, an attempt at the elimination of the foreign body. This is a congenital anomaly, and ought therefore, perhaps, not to be mentioned here.

Since an epithelium, in certain circumstances, exceeds its bounds, the conclusion is justified that there is a mechanism by which its excessive growth is normally checked and its cells kept within certain well-defined limits. It suggests that a congenital excess of tissue can be due to other causes than an abnormally large anlage or too great a vital energy of the cells. The restraining influences are of two kinds, general and local.

Physiologists teach that the general restraining influences depend upon the needs of the body. As long as an epithelium is present in sufficient quantity adequately to perform its functions, its cells do not undergo active proliferation, except for the small amount required to make up for physiological wear and tear. Should a great part of it be destroyed, the cells that survive proliferate and regenerate the tissue. An example of this is, as we have seen, the formation of multiple nodules of hepatic tissue in certain forms of cirrhosis of the liver. Very much the same kind of thing takes place when the function of an epithelium is impaired. Its cells proliferate, that the quantity of the secretion may balance its poor quality.

The local influences that restrain growth concern us more closely. They appear to depend upon the orderly correlation of epithelium and connective tissue. Ribbert<sup>9</sup> has pointed out that the cells of the epidermis proliferate when the superficial layers of the cutis are loosened by inflammatory exudate. This is equally true of the mucous membranes.

At a comparatively early stage of development the organs of the body acquire capsules, which inhibit their excessive growth. The epithelium never infiltrates the capsule while the latter is healthy. It is only after it is loosened by inflammation that the epithelial cells extend between its fibres. Should the capsule become defective, the parenchyma of the organ bulges into and enters the defect. It is usually shut off and its unlimited growth prevented by the formation of a fresh

capsule of inflammatory fibrous tissue. When, however, two different epithelia are brought into direct contact through a gap in the capsule, their apposed cells, no longer separated from each other by connective tissue, exert an irritating action on each other. This stimulates them to proliferate and to attempt to remove the foreign epithelium. Schmorl<sup>10</sup> is no doubt correct when he describes the invasion of the suprarenal by bile-ducts and liver cells as a foreign body reaction. Usually the cells of the suprarenal are the more vigorous of the two, and are therefore victorious in the struggle that takes place. They give rise to an accessory organ, whose growth continues, at an exceedingly slow rate, it is true, until a capsule has been formed around them.

Fig. 40 is instructive from another point of view. It is a typical instance of infiltration, such as is seen at the edges of every carcinoma, where invasion of neighbouring epithelium takes place. The tongue-like extensions of the hepatic cells closely resemble the familiar processes which every malignant new growth constantly sends outwards into the available tissue spaces. The cells in the present instance are far more typical in appearance than those of a carcinoma. This depends upon their infinitely slower rate of proliferation, which must have been very slow indeed. Opinions are still divided if the cells of blastomata acquire biological characters that are not shared by other cells. Ribbert pointed out again and again that no new qualities are assumed. Our specimen shows pretty conclusively that non-blastomatous cells possess the power to infiltrate their surroundings. It differs enormously in degree, but not at all in its fundamental characters, from the infiltration of malignant new growths.

6. *Heterotopic Lymph-nodes*.—In cases of carcinoma of the breast, in which the axillary lymph-glands have been extensively invaded and put out of action by the cells of the new growth, the formation of young lymph-nodes can be observed around the vessels of the areolar and adipose tissue of the axilla. The nodes often contain germinal centres. Such cases are instances of regeneration.

Lymph-nodes with germinal centres are not very rare in chronic inflammations of various parts of the body. They are always surrounded by a diffuse infiltration with lymphocytes, and can often be seen to be connected with a small arterial blood vessel. Greggio,<sup>4</sup> who studied them in the kidneys of rabbits that he had infected with *Staphylococcus pyogenes aureus*, concludes that they are developed from the adventitial cells of the vessels.

The thyroid gland is a favourite site for new formation of lymphoid tissue. References to this condition are numerous.

The fullest of these is in a paper by Simmonds,<sup>11</sup> who found lymph-nodes in 75 per cent. of exophthalmic goitres, in 15 per cent. of other enlargements of the thyroid, and in a small proportion of otherwise normal glands. He points out that they are very rare before puberty, and that they are therefore not congenital. He concludes that they are caused by local irritation.

I have, on several occasions, seen multiple isolated lymph-nodes, usually with definite germinal centres, in the atrophied

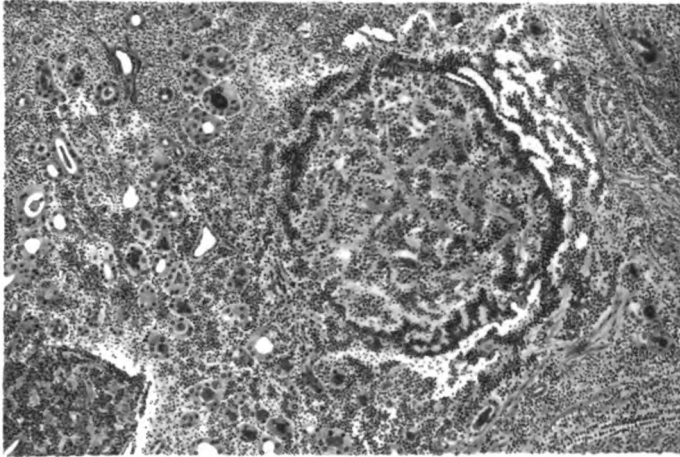


FIG. 41.

Heterotopic lymphoid tissue in thyroid. Magnif., 85.

and compressed thyroid tissue surrounding a large adenoma. Once these structures were present in an exophthalmic goitre. Fig. 41 represents a part of a uniformly enlarged thyroid. One lobe was removed, and presented identical microscopical changes throughout. There is a dense infiltration with lymphocytes, in which a few atrophic secreting vesicles remain. Numerous lymph-nodes, two of which are to be seen in the drawing, are scattered about everywhere. Their stroma is hyaline, and the larger one consists entirely of a germinal centre, surrounded by a ring of closely packed lymphocytes. In a second case, in which a small piece only was excised for diagnostic purposes, the structure was very similar. The infiltration with lymphocytes is present in the form of sheets and strands, between which groups of small thyroid vesicles

have persisted. Lymph-nodes with large germinal centres are very numerous. Both cases occurred in middle-aged women. There was considerable uniform enlargement of the gland, which was exceedingly hard. For this reason malignant disease was suspected.

There can be no doubt that this infiltration with lymphocytes is a part of a chronic inflammatory reaction, which has proceeded to the formation of nodes and germinal centres. The appearances that result from a pathological lesion are almost identical with those of the developmental anomalies discussed in Study III. This close resemblance suggests a similar ætiology for some of the latter. They may be the result of ante-natal inflammation, and not of excess of the

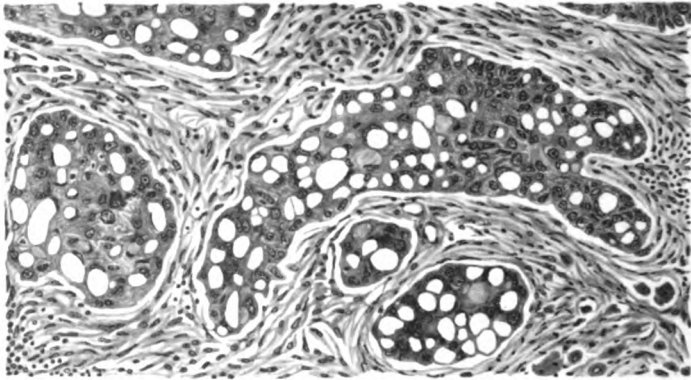


FIG. 42.

Epithelial fat cells in squamous carcinoma of tongue. Magnif., 170.

anlage of the lymphatic apparatus.\* I regard these lymph-nodes as a form of prosoplasia of the heterotopic lymphoid tissue.

7. *Fatty Changes of Epithelium.*—The histological appearances seen in many cases of extreme fatty infiltration of the liver are familiar. The epithelial cells are occupied by drops of fat, that coalesce to form a single large drop. This distends the cell, whose body is reduced to a narrow ring or linear membrane around it. The nucleus persists; it is flattened and often crescentic in outline, and pressed to the periphery of the cell by the globule of fat. Were it not for the presence of the portal canals, and of an occasional hepatic cell in which these changes are less advanced, it would be impossible in extreme

\* No blood disease was present in the cases described, nor did the tissues contain evidence of tuberculosis.

cases to distinguish such an altered liver from ordinary adipose tissue.

Fig. 42 illustrates these changes in an epithelioma of the tongue, other parts of which are extensively keratinised. Fibrillation of the epithelium is evident in several parts of the drawing, and indistinct prickle-cells can even be made out. Many epithelial cells are converted into typical adipose or "signet ring" cells. Had this change been more advanced, it might easily have become impossible to distinguish the papillæ of this epithelioma from lobules of adipose tissue.

It is not my present purpose to discuss the vexed question if this is a true conversion of epithelium into adipose tissue or mesenchyme, or if it is only an apparent one. The answer depends on whether it is possible or not to demonstrate squamous characters in the remains of the cells, and on whether they can return to their original condition. What I wish to point out is this. If it is possible for the cells of an epithelioma of the tongue to "mimic" adipose tissue so closely and effectually, it becomes highly probable that ordinary young connective tissue cells can do the same, and undergo differentiation into true adipose tissue in parts of the body where fat does not normally occur. Heterotopic adipose tissue in organs like the kidneys is therefore not necessarily due to a displacement of lipoblasts during development, but may legitimately be explained as an abnormal or heterotopic differentiation of the connective tissue of the organ.

A host of tissue anomalies has been described, which are almost invariably thought to be congenital. The evidence in favour of this view is, however, as invariably found to be very poor, if it is critically examined. This review of tissue malformations would be incomplete if they were not mentioned.

One of the most typical, and most often quoted and best known of these is the famous "cell-rest" of Bert and Fischer.<sup>2</sup>

It consists of a branched collection of small epithelial cells with indistinct outlines. They obviously correspond with those of the rete mucosum of squamous epithelium. There are indications of palisade cells at the periphery of the nodule. It is surrounded by scar tissue with numerous blood vessels and bundles of plain muscle, and was found by accident in the lung of a man of sixty-seven. The authors point out its similarity to a non-keratinised squamous carcinoma, and that it is probably non-malignant, since mitoses are absent, and there is no trace of an inflammatory reaction at its periphery. Chiefly on account of the presence of plain muscle they regard it as a congenital epithelial germ, hardly distinguishable from



a tumour. They dismiss the probability of its having been acquired as a result of an old inflammatory lesion, and express the opinion that metaplasia is only to be considered in tumour formation after the cell-rest theory has failed.

It appears to me that the only thing that is at all certain about this nodule is that it consists of squamous epithelium. The enthusiasm with which it has been greeted by subsequent



FIG. 43.

Nodule of squamous epithelium within hair-follicle. Magnif., 130.

writers, which, to do them justice, Bert and Fischer did not fully share, is quite unwarranted by the merits of the case. Bert and Fischer failed to show that it is not a fully established tumour, from which certain deductions can no longer be drawn, or that it could not possibly have been acquired. Why should the muscle that surrounds it not have resulted from proliferation of remains of the bronchial *muscularis mucosæ*, after it had been disorganised by an inflammatory reaction that has left no other traces behind it? Surely, it is but logical to accept metaplasia of epithelium in tumour formation in preference to the cell-rest theory, because the former condition is well known to occur in the bronchi (I have myself seen instances of it), whereas undoubted cell-

rests in an adult are only known in tuberous sclerosis, where their presence as such must be due to certain specific, but highly unusual, conditions. The case proves nothing.

This statement applies to the innumerable tumours in general, and the carcinomata in particular, that are assumed to have arisen in cell-rests on no evidence at all. Here the cell-rests are purely hypothetical, since they have grown into established tumours, and have long ceased to exist.

Fig. 43 represents a malformed hair-follicle, that was found accidentally in the lower lip of a man of sixty-two. It is bent, its papilla is small and atrophied, and the dermal *theca folliculi*



is much thicker than those of its neighbours. The centre is occupied by an oval nodule of large squamous cells. They correspond with those of the layer of prickle-cells. Fibrillation is apparent within them, and keratinisation has begun. The nodule is surrounded by a ring of large cells, that appear to form a kind of germinal layer to it. This is clearly a case of imperfect differentiation. Squamous epithelium has been produced, instead of the flakes that constitute the hair. I have succeeded in tracing this follicle in serial sections that were subsequently cut of the specimen. It passes into a neck, which is occupied by a dead hair. Had this anomaly been found in an infant or young subject, the adherents of Cohnheim's theory would have hailed it as a beautiful cell-rest. To judge by the case of Bert and Fischer,<sup>2</sup> those are not wanting who are prepared to do so in a man of sixty-two. But in my opinion the condition is clearly due to a disturbance of function caused by one of the numerous infections to which the skin and its appendages are liable.

It is possible that the pseudo "cell-rest" in Fig. 43 might have grown slowly to six or eight times its present size. In this case it would have produced atrophy of the greater part or of the whole of the follicle, and its disappearance, together with that of its neck. It would now be isolated beneath the epidermis. Again, it is possible that it might have formed the starting-point of a carcinoma. This would at first have been subcutaneous and quite unconnected with the epidermis. Yet again, it is possible that the small isolated subcutaneous carcinomata described by Borrmann<sup>3</sup> may have had a similar origin. There is no imperative need to assume with this author that they cannot possibly have originated otherwise than in a congenital "cell-rest."

### *Conclusions*

Certain anomalies, that arise in the tissues long after their development has been completed, are in every way comparable with congenital malformations.

Because of this, they can with propriety be called "acquired malformations."

They fall into the same groups as the congenital malformations, and can be subdivided into anomalies of bulk and of differentiation, and into those of position and the blending of tissues.

Their ætiology is often quite clear and obvious. Many of them are reactions to pathological conditions.

This interdependence of cause and effect constitutes the

strongest evidence in favour of their origin from cells that were previously healthy. It renders the assumption that these cells were the seat of a constitutional anomaly unnecessary and illogical.

Their close similarity with congenital anomalies suggests that the latter result from analogous causes: from a pathological environment and not from a *vitium primæ formationis*.

The structural similarity of certain acquired tissue malformations and of hamartomata raises the question if it is necessary to assume the presence of a congenital anomaly for all, or even for the majority of tumours, in accordance with Cohnheim's theory.

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## THE UREA CONCENTRATION TEST

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### I

A FEW notes of clinical and laboratory findings from one who has no claim to originality, or any personal bias towards this test, may be of general interest.

Since first reading Maclean and de Wesselow's paper in the *British Journal of Experimental Pathology* in 1920,<sup>1</sup> I have used their urea concentration test more or less as a routine in renal cases. The results from the first appeared to coincide with the clinical conditions, and the simplicity of the test was attractive.

During the last six months I have attempted a clinical criticism of the test, and have selected all the cases in which it appeared that the test would be interesting and of which one had reasonable grounds for estimating the condition of the kidneys on clinical findings or personal knowledge of the patient. If I may assume that the clinical opinions have been correct, I can say that the test has not once been at fault. These notes are an attempt to put the results on paper. The cases have been selected carefully for this investigation, but none have been rejected after the test has been performed. They are few in number, being only the notes of about six months' work, but, purporting merely to confirm the work of others, are enough to appear worthy of record.

### II.—TECHNIQUE

The patient drinks 15 grammes of urea, dissolved in 100 c.c. of water, having first emptied his bladder. At the end of one hour and again at the end of the second hour he passes urine. The total quantity of urine passed in the second hour is measured. Both specimens are tested in the usual way for the percentage of urea, the higher reading of the two being taken as the record of urea concentration. The urea sometimes causes diuresis, and, if more than 120 c.c. of urine is passed in the second hour, the result may be fallacious from this point

of view. The best time for the test is in the early morning; food may be taken, but fluid should be withheld.

Where the kidneys are healthy there should be more than 2 per cent. of urea in one or other specimen, probably not less than 2·5 per cent. There appears to be in healthy kidneys a fairly wide range of variations from about 2·5 per cent. to over 4 per cent. in some cases; and, on the other hand, with diseased kidneys, although readings below 1·5 per cent. are obviously bad, it may not be possible to be dogmatic about intermediate readings. But in my own cases, where the renal condition has been more or less stationary, the efficiency of the individual patient has seemed to be very nearly in accordance with the result of this test.

There does not seem to be the slightest risk that the urea will do the patient any harm, even if uræmia is present. Maclean discusses this fully.<sup>2</sup> The technique of this test has been discussed fairly frequently in the journals. I think the above routine, which has been adopted here, is the original test as published;<sup>1</sup> and it would appear to be efficient and practical.

In private practice the test is almost as easily carried out as in hospital. The urea can be put up in 15 gramme packets. One hundred c.c. is equivalent to about four ounces, which the patient can measure easily. If he returns the specimens in two 8-oz. medicine bottles, the quantity of urine in the second hour is estimated easily, because, if the bottle is appreciably more than half full, diuresis has occurred. There is no need to flavour the urea, and none of my patients have complained of discomfort.

For estimating the urea percentage Gerrard's ureometer is the best; but results quite reliable can be obtained with a Doremus apparatus, or one of its modifications. The hypobromite is the trouble outside a laboratory, because it does not keep. It is most conveniently made freshly by adding a 2 c.c. ampoule of bromine to about 25 c.c. of 40 per cent. caustic soda.

Estimations of the urea in the blood have been made in many of the cases; but it would increase the scope of these notes unduly to discuss this question. The blood urea is the guide to diet. Exceptional cases, in which a high blood urea has seemed to produce a fallaciously high reading for the urea concentration test in spite of diseased kidneys, have been recorded. In the limited number tested in this hospital such a fallacy has not been met with. The normal figure for blood urea is usually taken as something between 25 and 40 milligrammes per 100 c.c. of blood.

III.—CLINICAL CLASSIFICATION OF CASES

A. NON-NEPHRITIC ALBUMINURIA.

(a) *Functional Albuminuria of Adolescence.*

- (i) A. F., aged 17; was examined for some service, when albuminuria was discovered. Urine examined every day for a week showed trace of albumin in all afternoon specimens and in several, but not all, specimens passed on rising. Blood pressure 100 m.m.; blood urea 22 m.g. per 100 c.c. General health excellent. Urea test 3.1 per cent.
- (ii) W., male, aged 10; pale and anæmic. Afternoon urine showed trace of albumin, but three morning specimens were normal. Blood pressure 100 m.m. Urea test 3.3 per cent.

(b) *Cases of Leaky Kidney.*

- (i) E. J. P., male, aged 65; was refused for life insurance twenty years ago on account of albuminuria. I have known him well for fifteen years; he has had no symptoms of renal disease and leads an active life, although albuminuria is constant. Blood pressure 140 m.m. Urea test 2.4 per cent.
- (ii) B. S., male, aged 49; was refused for life insurance ten years ago. I advised no treatment. He had a general anæsthetic for anal fissure five years ago: he had then and still has albuminuria. Blood pressure 130 m.m. Urea test 2.8 per cent.
- (iii) C. W. L., male, aged 50; has had albuminuria for three years. Good general health. Blood pressure 130 m.m. Urea test 2.6 per cent.
- (iv) M., male, aged 44; tired and worried. Albuminuria discovered, but no other signs of renal disease. Blood pressure 125 m.m. Quite well after a holiday, but albuminuria still present. Urea test 2.6 per cent.
- (v) Mrs. S., aged 55; known to have albuminuria for several years. Seen on account of osteo-arthritis. No signs of renal or cardio-vascular lesion. Urea test 4.1 per cent.

B. CASES OF CHRONIC RENAL DISEASE.

- (i) B., male, aged 52; arteriosclerosis; uræmic and very ill; albuminuria. Blood urea 190 m.g. per 100 c.c. Diagnosis: interstitial nephritis. Urea test 0.8 per cent.
- (ii) H. J. R., aged 31; albuminuric retinitis; wasting. Blood pressure 220 m.m.; blood urea 69 m.g. per 100 c.c. (after being dieted). Diagnosis: interstitial nephritis. Urea test 1.5 per cent.

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- (iii) B., female, aged 15; marked dropsy; much albumin in the urine. Diagnosis: chronic parenchymatous nephritis. Urea test 1.4 per cent.
- (iv) Mrs. F., aged 48; has had albuminuria for several years. Blood pressure 180 m.m. five years ago. Chronic ill health and able to do little. Died two months after test was taken. Urea test 0.9 per cent.
- (v) Mrs. H., aged 51; has had albuminuria for fifteen years. Blood pressure ten years ago was 175 m.m. She is compelled to rest most of the twenty-four hours, but can do a little house work. Diagnosis: interstitial nephritis. Urea test 1.7 per cent.
- (vi) E. E., male, aged 48; was admitted for wasting. Investigated at first as an abdominal case; urine free from albumin. Eventually albumin discovered, and headache became pronounced. Blood pressure 180 m.m. Diagnosis: interstitial nephritis. Urea test 1.2 per cent.
- (vii) B., male, aged 62; came to hospital with albuminuric retinitis. Urine contained albumin. Urea test 1.3 per cent.
- (viii) H., signs of phthisis, with chronic nephritis supervening; albuminuria and œdema. Urea test 1.0 per cent.
- (ix to xiii) *Five Cases of Renal Dwarfism.* These cases all came to hospital in the first instance for recently developed genu valgum: they all have albuminuria and are typical examples of interstitial nephritis of children or adolescence, associated with bone deformity.
- (ix) W., female, aged 15; genu valgum and albuminuria. Urea test 0.8 per cent.
- (x) C., male, aged 14; genu valgum and albuminuria. Blood urea 202 m.g. per 100 c.c. Urea test 0.9 per cent.
- (xi) A. F., female, aged 21; genu valgum and albuminuria. Blood urea 97 m.g. per 100 c.c. Urea test 0.75 per cent.
- (xii) C. S., female, aged 12; genu valgum and albuminuria. Blood urea 154 m.g. per 100 c.c. Urea test 0.9 per cent.
- (xiii) I. F., female, aged 16; genu valgum and albuminuria. Urea test 0.7 per cent.

C. CASES TESTED TO EXCLUDE KIDNEY DISEASE. None of these patients had clinical signs which were evidence of kidney disease; but for some reason or other renal disease was discussed.

- (i) C.; gastric ulcer. Kidney disease discussed. Operation successful. Urea test 3.0 per cent.
- (ii) Mrs. F., aged 72; arteriosclerosis; signs of cerebral softening; urine normal. Urea test 3.6 per cent.
- (iii) W. R., aged 61; pale face; signs of degenerated heart muscle; urine normal. Blood pressure 125 m.m. Urea test 3.8 per cent.
- (iv) Mrs. S., aged 25; anæmia of Addison type. Albuminuria during pregnancy some months previously. Urine normal now and pulse low tension. Urea test 2.5 per cent.
- (v) M. S., female, aged 16; a case of adolescent knock knee. Urine normal. Tested by way of contrast to the renal dwarfs. Urea test 4.6 per cent.
- (vi) W. J., male, aged 26; mitral stenosis of rheumatic origin. Trace of albumin in urine. Blood urea 24 m.g. per 100 c.c. Urea test 2.5 per cent.

#### IV.—CONCLUSIONS

It will be seen that the healthy kidneys have excreted about 2.5 per cent. or more of urea, and that the diseased ones have failed to excrete so much as 2 per cent.

Although it is often fairly easy to distinguish the non-nephritic albuminuria cases, this urea concentration test is of practical value in helping to exclude kidney disease with confidence, more especially in the type met with in middle age, which I have included under the heading of Leaky Kidney, a nomenclature adopted in a recent discussion at the Royal Society of Medicine.<sup>3</sup> The excellent health of the two men, who have had albuminuria for ten years or more, is attributable to the fact that one has had the courage to leave them untreated.

The absence of albumin at certain times of the day and the clearing up of the albuminuria in some cases with calcium lactate are useful indications in albuminuria of adolescence; and the fact that some of the older patients are passing more globulin than albumin in the non-nephritic condition is a valuable aid in diagnosis, but the urea test is more reliable.

The interstitial nephritis cases recorded above have been fairly obvious examples, chosen deliberately to estimate the value of the test. But case (vi) of this series illustrates the insidious nature of the condition and the value of the test under such circumstances, because he was sent and for several days considered as a possible case of malignant disease of the

alimentary canal. The urine was recorded as normal when examined on arrival, and it was only after further consideration that the high arterial tension led to a second examination of the urine and the urea test, with a result of 1·2 per cent. One can look back on several cases in which this test would have cleared up a difficult problem, before some such sign as retinal hæmorrhages gave the key to the situation.

The renal dwarfs are sometimes very obscure cases with insidious onset, of which I have made notes in several papers.<sup>4</sup> One does not know at how early a stage of such an insidious condition this test would assist; but the readings recorded in these notes in five cases, all of whom, although in poor health, are getting about, are a further indication of the value of the test in diagnosis.

In acute and sub-acute nephritis the results of the urea test are in accordance with the clinical signs. In any individual case the percentage of urea in the urine after the test increases as the patient's condition improves.

In the toxæmias of pregnancy the test has proved of practical value; and the limited number of observations made here would seem to coincide with the results recorded by de Wesselow in a recent paper.<sup>5</sup>

A number of prostate cases have been tested by the urea concentration test and by estimation of blood urea, both of which are now used as a routine. No doubt clinical experience is the best guide and I have no clinical records of my own, but my colleague, Mr. F. L. A. Greaves, has found the tests very accurate indications for prognosis since they were introduced to this hospital.

These notes are from the physician's point of view; and I believe the test is a very valuable guide in diagnosis and prognosis. These cases were selected because there is little or no clinical difficulty; but in doubtful cases it has proved valuable in diagnosis and I believe it may be accepted as a fairly accurate test of renal efficiency. It is especially useful in those conditions in which renal changes are common but not necessarily constant,—for example in hyperpiesis. A good result with the urea test and a normal blood urea are signs that the prognosis is not very bad, even if the sphygmomanometer records an unduly high reading.

The urea in the blood is the guide to diet in kidney disease, and its estimation has made the whole question quite a scientific study, explaining the value of a high protein diet in the dropsical cases, but it is outside the scope of this paper. The urea concentration test, however, gives indications in these dropsical



parenchymatous nephritis cases, in which the urea in the blood is not increased.

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## EPIGASTRIC HERNIA

By ARTHUR F. HURST, M.D., Physician, and J. A. RYLE, M.D., Assistant Physician to Guy's Hospital.

As long ago as 1743 Garengcot <sup>1</sup> spoke before the Académie royale de Chirurgie on the digestive symptoms resulting from epigastric hernia. In spite of this, very little attention has been paid to the subject, and it is still true, as Lucas Championnière <sup>2</sup> wrote, that "there are few lesions, thanks to their small size and slight local tenderness, and the frequent obesity of the patient, which more readily deceive the physician by the intensity of the symptoms they may cause." We owe most of our knowledge on the subject to the investigations of Kuttner <sup>3</sup> in Germany and Moschcowitz <sup>4</sup> in New York.

Hernia of the linea alba is not uncommon, especially above the umbilicus, when it is called an epigastric hernia. It varies in size from a pea to a fist, but the larger sizes are always situated close to the umbilicus and are perhaps really umbilical hernias. The linea alba above the umbilicus is perforated by numerous vessels, which carry a prolongation of the transversalis fascia with them. The points of perforation form minute weak spots, and any increase in pressure within the abdomen may force some structure through. As the falciform ligament of the liver is attached just to the right of the middle line, and as it contains fat between its two peritoneal layers, some of this fat may be pulled through these holes, the fat of the hernia not being composed, as is generally believed, of omentum. Owing to the inelastic nature of the linea alba the hernia are rarely large. In every case the fat is continuous with the fat of the falciform ligament and is accompanied by a vessel. There is never a distinct hernial sac. They are thus fat-prolapses, and not true hernias. The latter, however, may occur, as in rare cases a fat-prolapse may become sufficiently large to pull out a secondary peritoneal diverticulum; the hernia in this way may even become strangulated.

### SYMPTOMS

Men, especially of the working classes, are more often affected than women. The hernia sometimes develops imme-

diately after rapid loss of weight. Thus Boas<sup>5</sup> says it is not uncommonly associated with cancer of the œsophagus and stomach. The symptoms are caused by dragging on the fat and peritoneum of the falciform ligament. The patient complains of eructation, nausea, and occasionally of vomiting, which may be the only symptom. This may occur only in certain positions and is likely to disappear on lying down. There is often vague discomfort, and sometimes attacks of cramp-like pain in the epigastrium, which do not bear any constant relation to food, but may increase or diminish after it. This was formerly believed to be due to a part of the stomach being in the hernia, but it is now known that this never occurs. It may come or go with changes of posture and is especially likely to occur after vigorous exercise.

A very small tumour is present in the middle line between the ensiform cartilage and the umbilicus, which often expands later towards the left; it is frequently very minute and difficult to feel, especially in the obese. It may be seen and felt most easily when the patient is standing. It is often irreducible. The protrusion itself and the opening through which it escapes are invariably very tender, which is an important point in diagnosis. Two cases have been described in which no tumour was felt, but the characteristic symptoms, and especially the local tenderness, were present. A vessel was found at the tender point and its ligature was followed by a cure (Moschcowitz).

#### TREATMENT

The fat is removed, the accompanying vessel ligatured, and the stump pushed back through the hole in the linea alba, which is then closed without opening the peritoneal cavity.

#### Case 1.—*Severe Digestive Symptoms caused by Epigastric Hernia*

Captain M. consulted me in December 1913 for digestive symptoms, which had begun immediately after an uncomplicated attack of enteric fever ten years before in South Africa. Previous to this he had been perfectly well. He complained of discomfort and a feeling of distension high up in the middle of the epigastrium, which was worse immediately after meals, but never disappeared completely. There was no pain or vomiting, and the discomfort, though present already before breakfast, never woke him in the night. It never radiated through to the back and was unrelieved by sodium bicarbonate. In 1909 his appendix had been removed for these symptoms, and he had had a course of treatment for ulcer, but in neither case did the slightest improvement result. He was always

better whilst resting, and the discomfort was aggravated by exercise.

I discovered a little fatty hernia in the linea alba in the upper part of the epigastrium. This corresponded exactly with the situation of the pain and was the most tender point of the abdomen. The x-rays showed that it was well above the lesser curvature of the stomach. Mr. F. J. Steward removed it, and the patient obtained complete relief. (A. F. H.)

*Case 2.—Small Fatty Epigastric Hernia with Symptoms suggesting Duodenal Ulcer*

Joseph C., *æt.* 52, an old soldier, presented himself at medical out-patients complaining of pains in the epigastrium which he had had for the past three years on and off, but which had become much more severe during the past six weeks. He experienced the pain two or three hours after food and had found that it was relieved by taking food or hot water. He also had pain nearly every night, which was relieved in the same way. In the last three months he had lost about two stone in weight. Before his severe pain had started he had particularly noticed that the action of stooping to lace his boots induced pain.

Physical examination showed a well-built, muscular type of man. The teeth were in a very bad state. There was pain on deep pressure in mid-epigastrium between the recti, and careful examination in this region revealed the presence of a small, flat, fatty tumour, which seemed to transmit a slight impulse on coughing; it covered an area about equal to a halfpenny in size, and was rendered the less conspicuous by reason of its flatness. The knee and tendo-Achillis jerks were present but sluggish. There were no signs to suggest a diagnosis of tabes dorsalis. The blood was taken for a Wassermann reaction in view of certain suspicious inguinal scars, but a negative report was returned.

The fæces obtained at out-patients, (where, however, they can never be regarded as very reliable,) gave a strongly positive guaiac test and a blood spectrum. The x-ray report after a barium meal stated: "No definite evidence obtained of organic lesion of stomach or duodenum. Hypertonic type of stomach. The spasticity seen in the neighbourhood of the pylorus is often associated with lesions of the biliary tract." Patient failed to swallow the gastric tube. After the mouth had been cleared, patient was admitted for operation. Mr. E. G. Slesinger operated and removed a small fatty hernia of the extra-peritoneal fat which was causing traction on and dimpling the parietal layer of the peritoneum. At the same time a laparotomy was performed, but no signs of disease of the stomach, duodenum, appendix, or gall-bladder being observed, the abdomen was closed. The patient experienced no further symptoms

after the operation, and after a month's convalescence reported again at out-patients, having gained a stone in weight and feeling quite well, and able to deal with his food normally.

(J. A. R.)

It would seem probable in this case that the symptoms were dependent on reflex pylorospasm due to irritation of the parietal peritoneum, akin to the pylorospasm encountered in some cases of appendicular and gall-bladder disease. The case also exemplifies the existence of reversible reflexes between hollow viscera and the parietes. The hyperalgesia of the extra-peritoneal tissues in gastric and duodenal ulcer is well recognised, but instances of increased excitability of the pyloric musculature due to painful stimulation of the parietes are rare.

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## TWO CASES OF TRAUMATIC THROMBOSIS OF THE BRACHIAL ARTERY DUE TO PRESSURE OF A CRUTCH

By JOHN RYLE, M.D., Assistant Physician, Guy's Hospital.

WITHIN a space of three months two cases have presented themselves among my out-patients showing complete obliteration of the radial and brachial pulses on one side, and giving histories which left no reasonable doubt that the brachial artery had in each case become occluded as the result of damage due to prolonged crutch-pressure.

While musculo-spiral injury from this cause is well recognised, arterial damage is so unusual, and at the same time likely to prove so much more serious in its consequences to the patient, that it seemed worth while placing the notes of the two cases on record. They should certainly serve as a further argument in favour of employing, where possible, the more modern crutch popularised during the war, in which arm-pit pressure is wholly avoided.

*Case 1.*—John B., aged 61, a clock-repairer, has had a completely paralysed right leg since early childhood, probably as the result of anterior poliomyelitis. For fifty years he has used a right crutch. A year ago he began to notice weakness and aching in his right wrist. Latterly this has become worse. While using the crutch the right forearm and hand become pale and cold and very painful, and when the circulation is permitted to return by relinquishing the crutch, "pins and needles" sensations are experienced. On examination just after arrival at the hospital the hand and fingers were "dead white" and cold. There was no pulsation in the radial or brachial arteries, and the latter could be felt as a hard cord of about the thickness of a little finger. There was a slight degree of wrist-drop and a feeble supinator jerk on the affected side. Blood-pressure in the left arm was 170 mm. systolic, and 80 mm. diastolic. The heart showed a triple rhythm and extra-systoles were frequent. While under observation the hand became flushed and pink again, and during this period the pain was obviously very severe.

In this case the age of the patient, the blood-pressure and other cardio-vascular signs pointed to the presence of arterial atheroma, and it seemed reasonable to suggest that the artery,

which had borne the crutch-pressure well in earlier years had finally succumbed to the combined processes of sustained trauma and degenerative disease.

*Case 2.*—William S., aged 35, a tailor, had infantile paralysis at the age of two years, and this has left him with a complete flaccid paralysis of both legs and great deformities of the trunk and chest wall. He has used crutches for as long as he can remember and is quite powerless to mobilise without them. He states that the left crutch has always taken more of his weight than the right. He complains of stabbing pains in the left forearm after using the crutches, which travel up to the shoulder; his hand then becomes white, cold and useless. These symptoms have been present for one week only, but he has noticed them in slighter degree on previous occasions. Examination shows the left hand, and particularly the thumb, to be paler and colder than the right. The radial and brachial pulses are completely absent, and in fact no pulsation below the subclavian can be felt. There is no muscular wasting, no drop-wrist, and supinator, biceps and triceps jerks are equal on the two sides. There is a sub-ungual whitlow on the left ring finger, which has resisted treatment for a long time. The radial artery can be felt as a small cord. Systolic blood-pressure is 130 mm. of mercury and there are no other signs of cardiovascular disease. Patient's general health in other respects is good.

In this case the trauma seemed to be the only obvious factor, and it is a matter for speculation why, after so long a period of years, the artery should have suddenly succumbed.

The tragedy in each case was the same, since one had to advise a man, whose activity and livelihood were dependent on his power to move himself, to abandon the only means of locomotion which he possessed. I am hopeful that after a period of rest it may be possible for them to learn the use of the modern type of crutch, but even so I should be afraid that the muscular effort may have the same effect on the circulation and efficiency of the arm, which is seen in the leg in sufferers from intermittent claudication. I should mention that in neither case could I find anything to suggest the presence of an aneurysm, nor were there any signs of interference with the venous return.

# CHRONIC OBSTRUCTION OF THE DUODENUM BY THE MESENTERIC VESSELS (CHRONIC DUODENAL ILEUS)

By ARTHUR F. HURST, M.D., Physician to Guy's Hospital.

It is now generally agreed that the acute dilatation of the stomach, which is a rare complication of abdominal operations and of various acute and even chronic diseases, is due to

obstruction of the third part of the duodenum by the superior mesenteric vessels. In May 1914 I met with a case in which chronic obstruction of similar origin appeared to be present, and a year ago a second case came under my observation (Fig. 1). This condition has been described by a number of American and French authors, especially by Codman, Staveland, Kellogg and Villette, and by Devine of Melbourne. It does not appear to have been recognised in Great Britain until Wilkie published a paper on "Chronic Duodenal Ileus" in October 1921. He gives an excellent account of the condition from his observations on eleven cases, which he had recognised

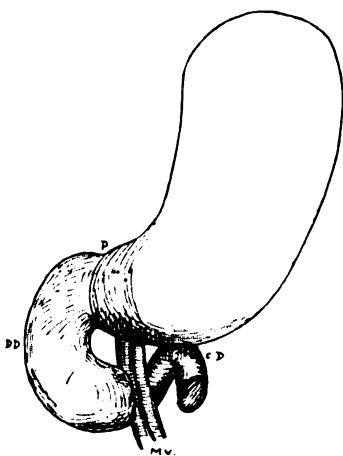


FIG. 1.

Diagram of Chronic Duodenal Obstruction. P., pylorus; D.D., dilated duodenum; M.V., mesenteric vessels obstructing the duodenum; C.D., collapsed duodenum beyond obstruction.

at operation, and Lockhart Mummery has this year described a further case.

## ÆTIOLOGY

The third part of the duodenum is normally compressed and narrowed to a slight extent where it is crossed by the root of the mesentery. The degree of obstruction must be increased in visceroptosis by the drag of the dropped intestines on the mesenteric vessels. This cannot, however, be the only factor,



or the condition would be more common than it is in women with weak abdominal muscles, and there was very little evidence of visceroptosis in the first of my cases. The congenital factor may sometimes be excessive mobility of the proximal colon, especially if it becomes associated with constipation.

#### SYMPTOMS

There is generally a history of indigestion dating from childhood. The patient complains of epigastric discomfort, which develops directly after meals. It is aggravated in the erect position and on exertion, and is relieved on lying down. There is often much complaint of flatulence, which is more due to aërophagy than to gastric fermentation. Sometimes "bilious attacks" with pain, nausea, and vomiting, which are followed by improvement in the digestive symptoms lasting for several days, occur periodically.

When the pain is present, the epigastrium is full and tender, especially over the duodenum; this can be demonstrated very clearly if the patient is palpated under the screen during an x-ray examination after a barium meal.

In my two cases a definite diagnosis was made with the aid of the x-rays before operation. As Wilkie points out, the obstruction may be intermittent, so that an x-ray examination made during an interval of freedom from symptoms might show nothing abnormal. This is another example of the errors which may arise from drawing conclusions from negative results of investigations into digestive cases carried out during a quiescent period.

#### COMPLICATIONS

Duodenal stasis, resulting from obstruction by the mesenteric vessels, must predispose to the development of a duodenal ulcer, if the other conditions necessary for its formation are present. It is, therefore, not surprising that a duodenal ulcer was found in three out of Wilkie's eleven cases. In some cases the violent peristalsis in the dilated duodenum causes the pylorus to become incompetent, so that the contents of the stomach and duodenum flow freely into each other. The gastric stasis, which is associated with the duodenal stasis when this occurs, must favour the development of a gastric ulcer, and one was found in one of Wilkie's cases.

If a gastro-enterostomy is performed for an ulcer in the presence of unrecognised chronic obstruction of the duodenum, a vicious circle is likely to develop, as Wilkie has pointed out.

It is possible that the greater frequency of acute dilatation of the stomach after operations on the gall-bladder than after other abdominal operations may be due to acute dilatation developing on the top of chronic obstruction of the duodenum, which must predispose to infection of the biliary tracts.

#### TREATMENT

Treatment by posture and the use of an abdominal support may lead to complete recovery, as in my first case. In my second case improvement was only temporary. Under these circumstances a duodeno-jejunostomy should be performed, in order to drain the dilated and obstructed duodenum into the jejunum beyond the obstruction. This operation was first performed by Staveley in 1908 and was used by Wilkie in five of his cases. A gastro-enterostomy, though successful in Mummery's case, is not so obviously indicated, as unless the pylorus is incompetent, the duodenum will not be drained, and with a duodeno-jejunostomy there is no possibility of a vicious circle, or of such complications as intestinal dyspepsia, diarrhoea, and gastro-jejunal or jejunal ulcers developing. The dilated duodenum is always found at operation to be hypertrophied and is in marked contrast to the remaining portion of the third part of the duodenum and the jejunum, which are thin-walled and collapsed.

#### Case 1.—*Chronic Obstruction of the Duodenum by the Mesenteric Vessels: Recovery following Postural Treatment*

Mr. C., aged 37, had had two or three attacks a year, for the last five years, of violent pain in the umbilical region, unaccompanied by vomiting or pyrexia. When I first saw him in May 1914, the attacks lasted about a week, the pain being present all day, but he was relieved for about half-an-hour by drinking a little milk. It also disappeared rapidly on lying down, and was consequently never present during the night. An attack was particularly likely to develop after a period of physical over-exertion, especially if accompanied by worry.

The patient had feeble abdominal muscles and a somewhat pendulous abdomen, but nothing else abnormal was found on physical examination. The x-rays showed that the stomach emptied itself with considerable rapidity, but was otherwise normal in every way. The duodenum was slightly dilated and there was obvious difficulty in passing through the duodenum when it crossed the middle line (Fig. 2). This was at once overcome by raising the stomach by means of the hand placed so as to support the lower part of the abdomen, and also on lying down.

I diagnosed the condition as chronic obstruction of the duodenum by the mesenteric vessels, this being only present in the erect position when the vessels would be dragged upon by the dropped small intestine. The patient was taught abdominal exercises and given an abdominal support. He was advised to lie down and take a little milk immediately he thought an attack was about to develop.

As a result of this treatment his symptoms disappeared. He served during the war in Mesopotamia and has remained in the best of health up to the present time.

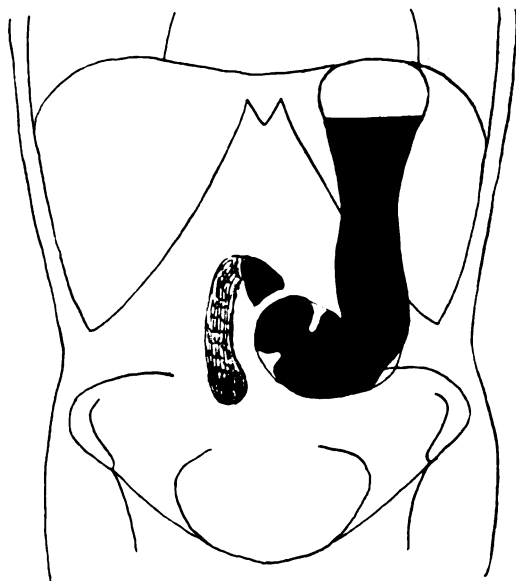


FIG. 2.

Duodenal obstruction by mesenteric vessels.

*Case 2.—Chronic Duodenal Obstruction by Mesenteric Vessels :  
Duodeno-Jejunostomy : Recovery*

Miss W., aged 29, had had a tendency to pain in the epigastrium for as long as she could remember. In 1914 she developed pain in the right iliac fossa, which disappeared together with her epigastric pain after her appendix was removed in 1916. The epigastric pain returned in July 1916, after a period of considerable physical fatigue. The pain was now almost constant during the day and was often associated with nausea, but no actual vomiting. Improvement always occurred after a short rest in bed; an abdominal support gave no relief. I first saw her in August 1921. She had lost a stone in weight in the last two years. The pain had never had any definite relation to food, but it was always aggravated by standing and fatigue and relieved

by lying down. The x-rays showed that her duodenum was greatly dilated, apparently as a result of obstruction where it is crossed by the mesenteric vessels. Violent peristalsis was observed which moved the contents of the duodenum rapidly backwards and forwards, but the whole of the opaque meal had passed out of the stomach and duodenum within five hours. The duodenum, when visualised with the x-rays, was found to be very tender. I diagnosed obstruction of the duodenum by the mesenteric vessels, and postural treatment was tried together with the use of an abdominal support. After temporary improvement the condition relapsed, and in March 1922 an operation was performed. The duodenum was found to be dilated and congested, but no ulcer was present. It was clear that it had been obstructed by the mesenteric vessels when the erect position was assumed. A duodeno-jejunostomy was performed by Mr. Taunton of Chatham. Complete relief followed, and when seen in July, 1922, the patient felt perfectly well, and the x-rays showed that the contents of the duodenum now flowed freely into the jejunum, although the duodenum was still somewhat dilated.

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## FIVE CASES OF PERFORATION OF THE LARGE BOWEL

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Cambridge.

THE five cases reported below are not rarities, for they may very well be met as emergencies in the practice of any surgeon, but they are somewhat out of the ordinary. They were considered as of especial interest at the time they were seen, and are alike in that in all of them there was perforation of the large bowel; in one case this was from injury, in the other four from disease. The cases are reported in their order of incidence.

### Case 1.—*Rupture of a Stercoral Ulcer of the Pelvic Colon*

On October 6, 1917, near on midnight a medical practitioner in the town asked me to see an abdominal emergency, which he said called for immediate surgical interference. As we went to the case I was given the history that that same afternoon at 4 p.m. the patient, a woman of middle age, had been taken with sudden abdominal pain. The onset of the pain was associated with vomiting. The attack was sudden and inexplicable. It was countered by the universal domestic panacea for abdominal pain—a dose of castor-oil. This was retained. Hot-water bottles and the recumbent position failed to relieve, but it was not until night was advancing without relief that the doctor was sent for. He wasted no time, but, realising the gravity of the position, came at once for me. When we saw the woman together, she presented the picture of an acute abdomen due to the rupture of a viscus. The abdominal wall was rigid all over, the liver dullness had gone, distress and foreboding were written on her face. The pain was complained of chiefly on the left side of the abdomen, and this side was more tender on attempted palpation. There was relative distension of the sub-umbilical part of the abdomen. The patient said that this had been noticed for a week.

When we attempted to localise the lesion we met with absolute negatives. No history of indigestion, vomiting, melæna, previous colic, jaundice or of any other abdominal

symptom or sign was forthcoming. In the course of inquiry the question of constipation was raised, but was denied at the time.

Immediate operation was advised and removal to a nursing home carried out without delay. Here the abdomen was opened on the assumption that most probably we were dealing with a perforated duodenal ulcer. When the peritoneum was incised brown fluid poured out in great quantities, and there was that local congestion which one associates with a perforated ulcer of the stomach or duodenum, and at first we felt quite convinced that this was the explanation of the attack. But after a cursory examination of the stomach and duodenum had failed to reveal any perforation, the anæsthetist said that there was a definite faecal smell present, and he thought it came from the fluid which had poured out of the abdomen. This was so, and on the strength of the observation the hand was passed down to the lower abdomen, where free faecal material was found. The incision was prolonged downwards and a hole found in the pelvic colon, which was brought to the surface through a separate opening in the left iliac fossa, and a colostomy established. The abdomen was cleansed as far as possible and drained, but every one felt that the condition was hopeless. Death occurred next morning about ten and a half hours after operation. There was no post-mortem. In the hurry of the operation and the shock of the finding, I failed to get a sufficiently accurate and permanent picture of the condition of the pelvic colon at the time of operation to speak with any confidence as to what the condition of the bowel wall was. We took it for granted at the time that we were dealing with a case of stercoral ulcer. The opening in the bowel was not a clean punched-out type of opening, such as is commonly found in the stomach or the duodenum, but was more irregular, and the fact that bits of faecal material were free in the abdomen shows that it was of some size. When first recognised, an attempt was made to close it in, but the stitches tore through, and as my assistant, an experienced man used to assisting at operations, said, "the bowel wall was rotten." At the same time there was no pericolicitis, no adhesions, no diverticulitis and no clear suggestion of a local gangrene or a diffuse infiltration of the gut wall. Save for the local lesion where the margin of the gut was thin, friable, and easily torn, the pelvic colon, beyond its congestion associated with the general peritonitis, presented no sign of any disease. The gut was handled, so that diverticulitis and neoplasm can be excluded. There was no history pointing to colitis, and no foreign body was found. The possibility

that a foreign body was the cause of the disaster cannot be excluded, but points against such an explanation are that the opening in the gut wall was ragged rather than clean cut, and that the abdomen was well mopped out and nothing found solid in character save faecal material and orange pips. Furthermore, when one thinks of the frequency with which foreign bodies are accidentally swallowed and the unconcern with which the experienced practitioner views such an accident, especially in contrast to the domestic agitation, one realises the rarity with which such an event is followed by disaster. Again, if perforation by a foreign body does take place, one would expect it to occur higher up than the pelvic colon, and to be rather of the nature of a localised perforation than immediate perforation into the general peritoneal cavity. This is the teaching of experience.

What is the evidence for a diagnosis of perforation of a stercoral ulcer? It is scanty. There was probably constipation, despite the denial, for the transverse colon contained much faecal material in lumps, although there was no evidence of any caecal distension. Again, her medical attendant afterwards told me that he had attended her in the past for certain vague pains, which he thought were due to some auto-intoxication, and which before this catastrophe he had suspected might be due to absorption from the bowel, there being no evidence of any other source of poisoning. On the other hand, she had no sallowness or muddiness of complexion, her tongue was clean and moist, and she gave no history of indigestion or flatulence, the common accompaniments of chronic constipation. Furthermore, the only cases of perforation of stercoral ulcers which I have seen have been in patients suffering from intestinal obstruction, have been caecal, and in the last stages of obstruction. In this case a rectal examination made previous to operation did not show a loaded rectum, and it could not be said that at the time of operation the pelvic colon was distended, but how much faecal material had been extruded into the general peritoneal cavity it is impossible to say.

The perforation may have resulted from an ulcerative process lasting some days, with gradual destruction of the separate coats of the bowel, or it may have been due to a local patch of gangrene involving all the coats of the bowel at the same moment owing to the blocking of a vessel from thrombosis. On the whole I am inclined to the latter view. It would explain the acuteness of the attack and the failure to localise. Furthermore, there is no need to invoke the serious degree of preceding constipation which one associates with a stercoral ulcer. The

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following case of acute localised gangrenous perforation of the cæcum shows that such a lesion can occur, although it is rare in the case of the bowel. Whether such a case can be compared with some cases of perforation of acute ulcers of the stomach remains a matter of speculation. It would not be wise to attempt any comparison with gangrenous patches in the appendix, which are rather comparable to the stercoral ulcers of intestinal obstruction or the gangrene of mesenteric embolism.

##### *Case 2.—Perforation of the Cæcum in an attack of Appendicitis*

An unmarried lady of 27, said to be suffering from gastric ulcer, after a night of abdominal pain and diarrhœa was at 7 a.m. taken with acute pain in the right iliac region more severe than any she had ever suffered from before. I saw her at 10 a.m., when she appeared to be in great pain, which she said was practically all over the abdomen, but the abdominal rigidity was definitely right-sided with a point of maximum tenderness just above and internal to the anterior superior iliac spine. The rigidity was not absolute, for the abdomen was inclined to relax if the examination was persisted in. Pulse was about 70, and temperature 99·4°.

She was moved into a nursing home, and at 12.30 p.m. I explored the abdomen with a provisional diagnosis of a leaking duodenal ulcer. I was influenced by her statement that she was shortly to be operated on for gastric ulcer on her return home to the south of England. In the cæcum was a perforation about the size of a pea with a blackish-green gangrenous area immediately surrounding it. The perforation was practically half-way between the base of the appendix and the line of the ileo-cæcal junction. Definite appendicitis of an acute catarrhal type was also present. Careful examination after its removal failed to reveal any trace of necrosis or ulceration. There was also no evidence that the appendix had been adherent to the focus of cæcal gangrene, for there was no lymph on the cæcum nor signs of adhesions having been separated. What the original position of the parts was I cannot say, for the pathological conditions were found by pulling up the cæcum into the wound, which had been placed rather high. The perforation in the cæcum was distinct and capable of allowing an easy flow of liquid fæces from the bowel, yet there was no evidence of pronounced peritonitis and no free fluid in the peritoneal cavity. This suggests that before disturbance the perforation was shut off by some localising adhesion, unless one believes that the diarrhœa, which preceded the perforation, had so



absolutely emptied the bowel that no leakage was possible. Experience would negative such a view, but the failure to find any suggestion of a lymph barrier around the perforation leaves any explanation of the facts very debatable.

In this case I am convinced we can exclude an ordinary stercoral ulcer, for I inquired carefully into the matter after she had recovered. She was a most intelligent woman and stated definitely that, far from being constipated, her bowels were always rather free. It seems probable that the pain and diarrhoea from about 10 p.m. until 7 a.m. were due to the acute appendicitis. The condition of the appendix was just what one would have expected after an attack lasting about fourteen hours. There is justification for believing that perforation of the cæcum took place at 7 a.m. The etiology of this small gangrenous focus in the cæcum remains obscure, and it is of interest to speculate whether the etiological factors were ultimately the same in these two cases apparently so diverse.

### Case 3.—*Traumatic Rupture of the Pelvic Colon*

During the evening of August 7, 1918, a girl of 30, cycling along a country lane, was run into by a pony-cart; one of the shafts perforated the abdominal wall just above the left groin. There was a large tear, through which the small bowel protruded. She was brought some distance from the country and admitted to hospital, where I saw her half an hour afterwards. She was very collapsed, and the house surgeon explained to me that he had given her digitalin, and that even with that she was too ill for any operation. This is not an uncommon attitude for the inexperienced man to take with regard to cases of profound shock. The girl did appear very ill; she was cold and practically pulseless. I told him, however, to give her some morphine and atropine and to get her body warmth back with hot bottles. I also ordered a hot saline enema. This, as it turned out, was a grave blunder. A cursory examination of the wound had left me with the impression that I was dealing with a lacerated abdominal wall with prolapse of bowel. As a matter of fact I was dealing with a case of rupture of the pelvic colon. Even supposing, however, that there had been no rupture of bowel at all, I think that with the injury in the region of the left groin or iliac region it would have been better to have given no fluid by the bowel, for it is better to avoid any sort of movement of the parts in the neighbourhood of an injury. When I first saw the patient I was afraid that internal hæmorrhage was the cause of her serious state, but further examination

negatived this view, for her mucous membranes were of a good colour, her breathing was rather the quiet, slow breathing of shock than the quick breathing of hæmorrhage, and she was quiet instead of restless and anxious. In response to the morphine and atropine and warmth her pulse improved, so that I felt justified in having her removed to the operating theatre. Here examination showed that the pelvic colon had been torn across, save for a small uniting band on the posterior wall at the mesenteric attachment. A Paul's tube was put into each end of the torn gut, a few bleeding points tied, the gut was fixed to the wound, the skin and muscles were brought together round the Paul's tubes, to shut in the wound and prevent prolapse, and the parts were packed round with gauze. The damaged gut and the rectum were empty. The normal saline solution which had been given by rectum was in the general peritoneal cavity. It was mopped out and the whole neighbourhood of the injury cleansed with hot moist swabs. I think it would have been better to have put in a suprapubic drain. On August 17 the patient had a swelling in the right iliac fossa, which was tender and fluctuating; it was associated with fever and was clinically like an appendical abscess. There was no pelvic element evident on rectal examination, and this was confirmed at operation, for a muscle-splitting approach revealed a collection of breaking down blood which had evidently not been got rid of at the first operation. It was drained and quickly healed so that in a short time the girl was well save for her two colostomy openings. She was advised to have them closed but refused, and for nearly six months tolerated the discomforts and drawbacks of these artificial openings. She then returned to hospital and had the openings closed. Prior to operation I did what I have done several times in similar cases, and what I have no doubt has often been done by others to further a successful issue, though I do not remember seeing any definite mention of it in any book. Several days before operation the skin round the openings is washed with plain soap and water, followed by ether, and then an ointment composed of equal parts of yellow oxide of mercury and zinc ointments (B.P.) is rubbed into the skin. This inunction is carried out night and morning and a layer of the ointment left on the surface each time. This layer is a surface protection; the ointment which is rubbed in fills up and renders the skin follicles antiseptic. Before operation the bowels were cleared by enema and no other preparation of the skin was made until immediately preceding the operation, when it was washed with soap and water first, followed by spirit, and finally painted with 2 per cent. picric acid. By using this

preliminary preparation and maintaining an antiseptic régime until the whole infected area has been shut away, I have been enabled to get union free from sign of infection following the closing of cases of artificial anus. I do not mean by this that I do not drain such a wound at all, but that in twenty-four or forty-eight hours I have been able to remove the drainage tube (which is only subcutaneous), and no pus formation has taken place. In this particular case the opening was closed in January 1919; this was the first time I used this antiseptic ointment method, and I am inclined to ascribe the absence of any infection of the wound and delay in healing to this small detail in preparation. It may be worth noting that an end-to-end anastomosis was made, not by preference, but to avoid any risk of tension, which would have resulted had the two ends been turned in and a lateral anastomosis performed.

*Case 4.—Perforation of a Malignant Ulcer of the Pelvic Colon*

This patient, a woman aged 62, was sent a distance of sixty miles and admitted to a nursing home in Cambridge. She arrived at 11.30 p.m., when I saw her for the first time. The history obtained was that for three months she had had "grumbling" pains in the abdomen, and for some time there had been constipation. There was no history of loss of weight, and the patient was found to be a stout woman of rather florid type. The history of the present attack was that on July 3 she was not feeling well and remained in bed. On July 4 at midday acute pain set in suddenly across the lower abdomen. The only time she was sick was after being given some medicine by the mouth, and since the onset of the pain there had been one rather loose action of the bowels. The nurse who came with her said that at the onset the pain was so severe as to cause collapse. She had some morphia given her to ease the long journey, and when I saw her at 11.30 p.m. on July 4 she was in quite good general condition. The pulse was 102, the temperature 101°; at 4 p.m. there had been no fever at all. On examination the abdomen was not rigid or hard, but in the lower half it was definitely tender on palpation. The upper half seemed normal. There was no abdominal distension. The tongue was clean and moist. On rectal examination there was great tenderness, especially on touching the back of the uterus in Douglas' pouch. The diagnosis was uncertain, and I could not make up my mind whether to advise immediate exploration or to wait. I had to remember that she was 62 and had travelled

sixty miles in a not too comfortable ambulance, that I knew nothing about her beyond her history and her immediate condition, but that, on the other hand, her relative comfort might be due to the morphia, and that if I left her it would probably be for a great number of hours. I sent for one of my medical colleagues, put the problem to him and asked him to give me his opinion. After confirming the clinical features of the case and discussing with me the significance of symptoms and signs, he advised waiting until the morning. This coincided with my own views. I felt that a night's rest would add to her chances of recovery, for any abdominal lesion present was probably local rather than general. My colleague and I met next morning. The report was on the whole quite good. There had been a fairly comfortable night with very little pain and no sickness. The tongue was still clean and moist, the temperature  $100\cdot6^{\circ}$ , but the sign which decided me that further waiting was inadvisable was that the pulse rate had risen to 124. There was still pain and tenderness across the lower abdomen, but some quite definite movement. There had been no action of the bowels, and the patient said she had not passed any flatus per rectum. My colleague made a rectal examination and found great tenderness everywhere in the pelvis. Micturition was normal and painless. We agreed that an exploratory laparotomy was justified, and this was performed without delay.

A sub-umbilical median laparotomy was performed. No free fluid was found in the abdominal cavity, nor was there any distension of the small bowel, but the cæcum, which presented in the wound, was very distended. The appendix was quite normal. We thus eliminated the diagnosis which was at the back of our minds—a pelvic appendicitis. The upper abdomen was now shut off, and the pelvis was explored. Pus was found, and at the level of the pelvic brim a growth of the pelvic colon, which had perforated, was discovered. My impression at the time was that the pus was not completely localised, and that there was rather a spreading purulent peritonitis, which had partially localised in the pelvis because of the patient's complete rest and the morphia injection. A colostomy above the growth and free drainage of the abscess were the obvious lines of treatment, so, after performing a left iliac-colostomy, the pelvis was mopped clean and drained by two tubes, one to Douglas' pouch from the lower end of the incision, the other through the posterior vaginal fornix. The patient made a steady and uneventful recovery and lived for about a year longer. At the end she gradually wasted away, and before death both the lines of drainage reopened and discharged, but this was unaccompanied

with any pain, and, as she was well nursed, with but little trouble.

This case was quite unique in my experience, and from inquiries I have made amongst surgical friends I find that such cases are rare. Growths of the large bowel, however, are common, and in practice are liable in my experience to be overlooked in the early stage of symptoms and signs, and also in the earlier stages of the later phase of obstruction. I have been so much impressed by both these points that I propose very briefly to make some reference to them without attempting any full discussion. In these remarks I am not including growths of the rectum, for these should be diagnosed with some certainty either by palpation or the sigmoidoscope. The history of diarrhœa, which, when analysed, is the passage at intervals of the mucus, sometimes blood-stained, which has been secreted by the growth or the bowel in its neighbourhood, is one of the clinical pictures which call for further examination. Another is the feeling that the bowel has never been properly emptied, or the home-made diagnosis of "piles" in an elderly man troubled with some loss of blood and sense of fulness. Such histories call for rectal examination.

My interest for the moment is rather with growths of the upper pelvic colon, and above this, especially in the splenic flexure, as when diagnosed in time they can be removed and the patient may live for many years. Metastatic deposits are late, warning symptoms often appear well in advance of a final obstruction, and yet a diagnosis is, so frequently, only made when a laparotomy is performed for obstruction, necessitating removal at a later operation, which may be impossible because metastases have formed. How are we to anticipate alike metastases and obstruction? I think it is by listening carefully to the history of increasing constipation, especially in elderly people, and realising that it may be a stage on the way to obstruction. If a patient, especially one getting on in years, says that he is getting constipated and finds that the dose of purgative requires gradually increasing, I think the safe plan is to put him under observation, and examine the motions both for mucus and blood. If either is present, or even if they are not present but the constipation is definite and difficult to overcome, a barium enema should be given and unless no obstruction or narrowing is discovered, the question of operation should seriously be considered. If there has been a definite attack of subacute obstruction, the bowels should be cleared out, a barium enema given for diagnostic purposes, and only the most definite negation should warrant proceeding no further. I have a

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recent case very vividly in my mind which emphasises these points.

A man of 40 was sent to me by his medical adviser with a history of two attacks of subacute obstruction. He was exceedingly well nourished, but had the prematurely aged appearance one not uncommonly finds in comparatively young people who are the victims of malignant disease. He was suffering when I saw him from constipation bordering on obstruction. He was sent into a nursing home, and with enema and purgatives the bowels were well emptied. He was then given a barium enema, and the picture was sufficiently clear in my opinion to justify advising an exploratory laparotomy, even in the absence of the convincing history of the two attacks of sub-acute obstruction which were forthcoming. However, he absolutely refused any operation and went back into the country.\* He then, as is usual when a real bad prognosis is given, sought further advice, but without letting his local doctor know, so that the consultant was handicapped by lack of any reliable history of events. The interesting thing to me was that the medical man consulted wrote to the local doctor a very full account of what he found and the grounds for his diagnosis. He decided that malignant disease was not present mainly for these three reasons : (1) the man's age, (2) the man's appearance, especially the fact that he had not lost weight and was exceedingly well nourished, and (3) the tumour palpable in the abdomen was not irregular or nodular. Now I cannot imagine a more unconvincing line of reasoning. Age is no bar at all. That growth is more common at a later period of life all acknowledge, but that it is rare at 40 is unfortunately not a fact. Within the last three years I have operated on malignant growths of the large bowel in women of about 40 years of age, and there is a man aged 28 in Addenbrooke's Hospital as I write with an inoperable malignant growth of the rectum. With regard to the second point, a growth of the large bowel can advance to the stage of absolute obstruction and the patient not lose in weight at all. This has led to grave error, not only in misleading people into a false sense of security, because it is a common belief that any one the victim of malignant disease must be wasted, but it may make the clinical picture in regard to palpation and estimation of abdominal distension exceedingly difficult. I have in my mind two such cases, in which it was impossible to decide whether there was any abdominal distension : probably there is none in such cases, for the pressure

\* This patient died from acute obstruction within three months of the consultation.

of gas in the bowel may be incapable of distending an abdominal wall which has a layer of fat on its surface three or four inches deep. There is an old expression in country places—"Feeding a cancer"—and some of these patients with the most pronounced disease have large appetites and keep up their weight, and I have even heard it said by friends that the weight has increased.

About a year ago I saw a man of 48, living in a very intellectual circle and of great intelligence himself, who never sought advice until he had absolute obstruction. One of his closest acquaintances, a college colleague, told me that he had not wasted at all, and the only thing that had been noted was that he had an inordinately large appetite. His was a case where waiting for visible and palpable distension of the abdominal wall would have been fatal. There were between two and three inches of fat on the abdominal wall, and up to the time of operation this appeared relatively soft. Fortunately he had the classical symptoms: inability to pass flatus and recurrent attacks of mild colicky pains. This man, it may also be noted, was never sick up to time of operation, and this is not at all an uncommon history. Usually, however, once obstruction has set in, there is a distinct reluctance to take food, and there is much wind brought up. It should be remembered that the absence of vomiting does not exclude absolute obstruction of the large bowel. The common teaching is that the lower down in the large bowel the obstruction, the less likelihood there is of vomiting. This statement should be followed by the warning that 95 per cent. of growths of the large bowel are between the left iliac crest and the anus. Remembering this, the absence of vomiting should not be allowed to prejudice the mind against a complete obstruction.

The third point mentioned was that the tumour in the abdomen was not irregular or nodular. Now I can fully confirm that the palpable left iliac tumour was not irregular or nodular, as palpated through the abdominal wall, but when one is palpating an inch of tissue before anything intra-abdominal is reached, it is probable that only the most gross irregularities are appreciable, and especially so if the muscles are slightly resistant. It is also difficult to decide whether one is palpating an edge of muscle, a sulcus in between muscles, or something inside the abdomen, and when one has decided that the bowel is being palpated, it is difficult to be certain whether the bowel is palpable because it is loaded with fæces, or because it is distended above a more distal obstruction, or because the gut is thickened from hypertrophy of its coats. In this particular case I examined the man several times both before and after

enemata and purgatives, and could never make up my mind that anything I felt gave a reliable clue to his disease. My feeling on the matter is that when the tumour is unmistakably palpable it is beyond cure because of glandular enlargement, neighbouring adhesions and thickening of peritoneum.

There is no need to emphasise the fact that tumours of the flexures are beyond palpation, nor the well-known significance of a variable tumour produced by intermittent distension of a hypertrophied bowel behind a stricture.

To sum up: neither age, apparent good nourishment, nor the dubious results of palpation should prejudice us in arriving at a diagnosis in the presence of increasing constipation, requiring increasing doses of purgatives, despite a reasonable dietary and mode of life. To anticipate trouble the whole armamentarium of diagnosis should be brought to bear. Again, subacute obstruction should harden our hearts against any simple functional condition, and the failure to pass flatus with the presence of colicky pains should make us decide that the hour of absolute obstruction with the necessity for immediate operation has come. One good dose of castor oil and one good enema should usually enable the diagnosis to be clinched one way or the other, and neither age, weight, nor the questionable results of palpation should turn us aside from advising early exploration.

*Case 5.—Perforation of a Malignant Ulcer of the Splenic Flexure into the Retroperitoneal Tissues*

This patient was admitted to hospital suffering from a large left-sided perinephric abscess; his temperature showed the wide fluctuations characteristic of a collection of pus. The abscess was opened, the pus having the typical smell of a *Bacillus coli* infection. The interest of the case was that we anticipated the further history, diagnosed a malignant growth of the bowel, which by perforating retroperitoneally had lead to the abscess, and foretold the probability that sooner or later obstruction would set in. This proved to be the case, and ten days after operating on the abscess, a left para-rectal incision was made to open the abdomen, and a ring carcinoma of the splenic flexure found. This was palpated but not inspected, so that no local investigations of the site of perforation were possible. The obstruction was only subacute, and it was possible to do an anastomosis between a loop of the ileum and the pelvic colon. This entirely relieved the condition, and during the remainder



of the time the patient was in hospital the bowels opened well; but of course the operation was only a palliative one. This is an interesting case when contrasted with the case of intra-peritoneal perforation of the growth of the pelvic colon. In neither case was a close investigation of the locality of the perforation made, and whilst such cases are labelled "perforation of a malignant ulcer," it is quite possible that they are perforations of ulcers situated above but in the immediate area of the upper limit of the malignant ulcer and produced by stagnation and distension. I have never had the opportunity of closely investigating such a case, so cannot speak with certainty about the locality of the perforation.

It was noted as an interesting fact in this case that the upper part of the small bowel was empty and collapsed. It throws a light on the phenomenon of the late onset of vomiting in these cases. The obstruction here was absolute, but it had come on gradually, and although the lower end of the ileum was distended and congested, the jejunum was empty, collapsed, and pale. It would suggest that the bowel has some capacity to resist distension. Hypertrophy of the bowel wall above the growth is a gradual process, extending backwards but not preventing a concomitant distension of the lumen. This observation suggests, however, that distension is localised and is not purely mechanical, but that as each segment of bowel is brought into action it distends to contain gas at the same time that it hypertrophies to aid in overcoming the peripheral resistance. When with the open abdomen the distended cæcum and the lower ileum dully congested and at least twice the lumen of the contracted pelvic colon are seen, it is clear that the condition of the ileum and cæcum by the time that the jejunum is becoming distended and vomiting is imminent, is such that their vitality is certainly endangered. This emphasises the inadvisability of waiting for vomiting as a sign of obstruction.

In conclusion I will briefly describe a case, which may be said to be the opposite in its clinical manifestations to those just referred to. This was a case of obstruction high up, where vomiting was the outstanding feature, and an enema resulted in such a satisfactory action that it was taken for granted that no obstruction could be present.

A man of 58, hitherto in good health, was seized with pain in his abdomen after breakfast on January 19 of this year. He sought no advice until the evening of the 21st. All that day he had been sick. His doctor found him with nothing definite in the way of signs, but with the history of vomiting that day

and constipation. There was no fever, his pulse was good, and his general appearance was that of a healthy country man. Obstruction was seriously considered, and an enema ordered with the understanding that unless entirely satisfactory further steps were to be considered. The report came that the result of the enema was entirely satisfactory and that the patient was much better. There also happened to be a lull in the vomiting, so that, coming at a time of great stress, the doctor thought he might very well avoid another country journey that night. But the enema had only emptied the large bowel well below the obstruction, although it produced a fairly large and satisfactory action. In a short time vomiting set in again, and in the late morning of the next day it had a definite faecal odour. He was sent into a nursing home, where he came under my care, and where the difficulty in diagnosis presented itself very forcibly to me. I accepted unconditionally the history of faecal vomiting. When I saw the man, there was little else to go upon. He had not vomited since admission, his general condition was quite good, and his pulse a little faster than normal. I thought his abdomen was slightly distended, but he assured me that it was not. It was supple and there was no pain. Rectal examination was negative. However, accepting the history of vomiting, with a pulse rate between ten and twenty above the normal, I thought I had better take the abdominal distension at my own valuation rather than that of the patient. I opened the abdomen expecting to find obstruction associated with some form of malignant disease. Instead I found the simplest form of peritoneal band obstructing the bowel quite high up, with the gut above thinned out by distension, uniformly congested, bruising badly if touched, and with the faint odour which one attributes to the early escape of *B. coli* infection from the bowel lumen to the peritoneal cavity. There was extreme distension of these coils and difficulty in getting them back into the abdomen. The patient died some twelve hours later.

## SOME NOTES ON DENTAL HISTOLOGY \*

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For the purposes of studying the soft dental tissues, no difficulty is experienced in providing sections of normal pulp, but for the examination of the periodontal membrane and gum, recourse is had to the mandible of the cat, so that the tooth can be looked at *in situ*. The first photograph (Fig. 1)

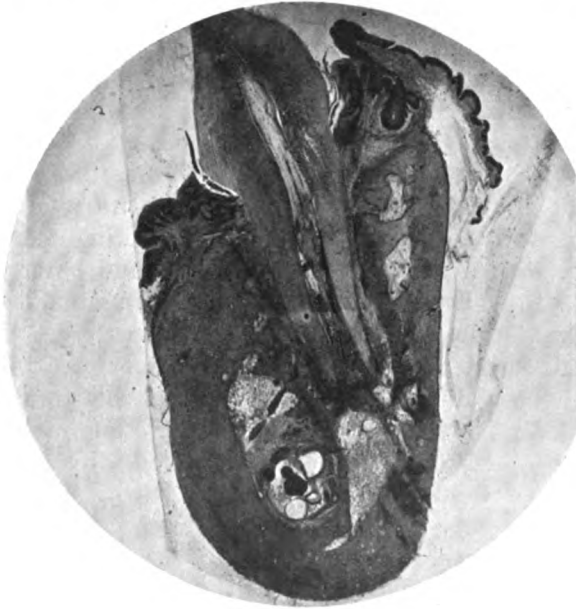


FIG. 1.       $\times 8$ .

Decalcified section through mandible of cat, molar region.

is a section through the molar region magnified only about eight times. This, of course, is not enough to show minute details, but is of value in studying the architecture of the mandible. The tilting of the tooth inwards is well marked, and the inferior dental canal is large and situated well to the inner surface of the tooth. The difference between the outer and inner plates of the alveoli is obvious, but shows still better

\* Founded on a paper read before the Odontological Section of the Royal Society of Medicine in May 1922.

in Fig. 2, which is a section through a pre-molar. Here the difference between the two plates is very well marked. The compact bone externally and the cancellous internally are well differentiated, the latter as in the human mandible is more condensed in the alveolar portion than in the base. The inferior dental canal is immediately under the root of the tooth and is surrounded by a distinct area of compact bone. Cunningham, in his description of the human canal, says it has no definite wall, but it will be agreed that in the cat at any rate it possesses one.

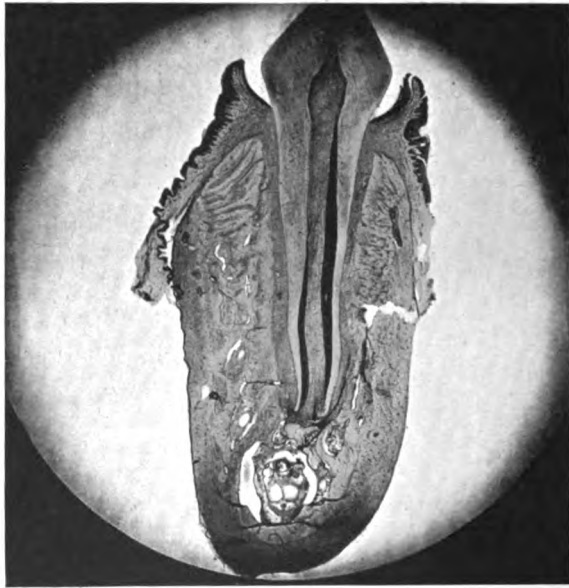


FIG. 2.  $\times 8$ .  
Mandible of cat, pre-molar region.

Fig. 3 is a photograph of the gum, periodontal membrane and alveolus more highly magnified, and shows the intimate relation these tissues bear to one another. The direction of the fibres of the periodontal membrane can be well seen, those nearest the crown having a direction upwards away from the alveolus and forming part of the supporting structure of the gum. The next set of fibres pass obliquely downwards and outwards to the alveolus, where they are attached to the highest point, but you will see that a number of these fibres run down the outer side of the alveolus to be attached some distance away from the tooth. The direction of the fibres gradually becomes transverse and two large blood vessels can be seen, one of which is issuing from the bone; the direction



FIG. 3.  $\times 25$ .

Pre-molar of cat, gum, periodontal membrane and alveolus.

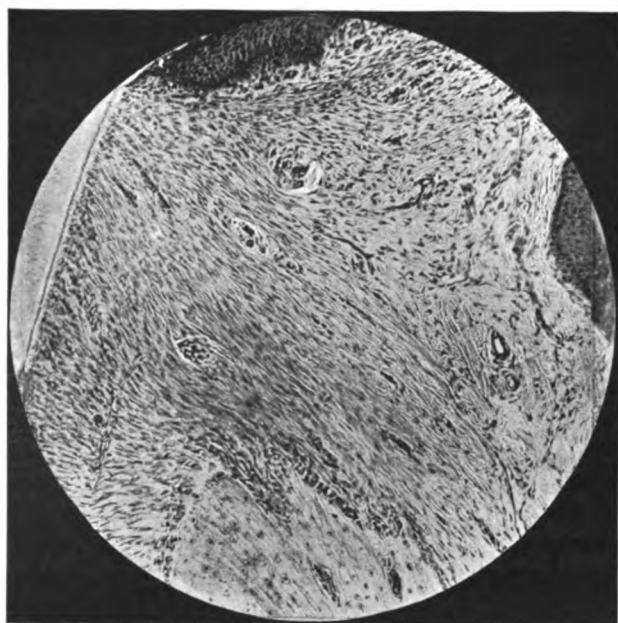


FIG. 4.  $\times 120$ .

The same.

of the fibres then gradually becomes oblique, but assumes the opposite direction, namely, upwards and outwards.

Figs. 4 and 5 are higher magnifications at A and B, and show the direction of the fibres rather better.

Fig. 6 shows the inferior dental canal with its contents as well as the compact bone forming its wall.

Fig. 7 represents a section of normal pulp stained with gold chloride, and shows two nerve bundles breaking up into fan-

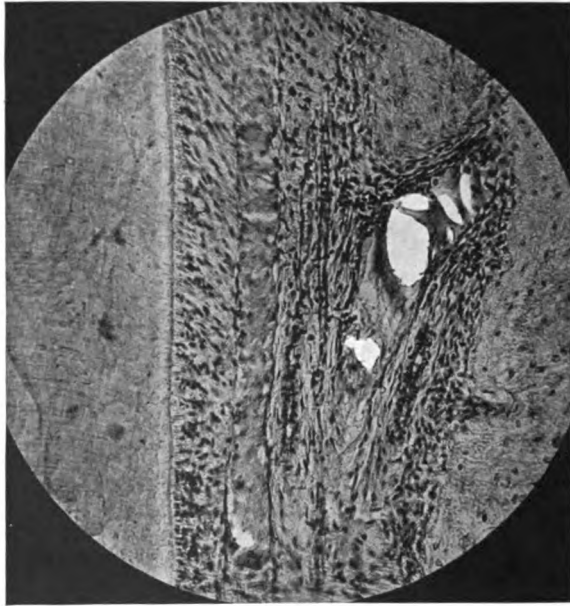


FIG. 5.  $\times 120$ .

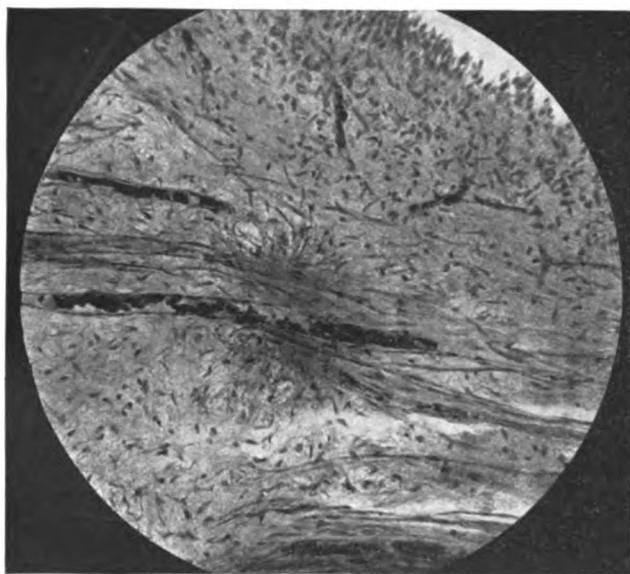
Pre-molar of cat, periodontal membrane and blood vessels.

shaped masses of fibrils in close proximity to some blood vessels.

Fig. 8, from a section stained with iron and tannin, shows the dentinal processes of the odontoblasts drawn out of the tubules.

An accident that may happen, and probably occurs more frequently than might be imagined, is the removal of a pre-molar when extracting a temporary molar. Fig. 9 is a photograph of such a specimen from a patient aged six years, the pre-molar measuring about 3 mm. It shows the pulp canal of the temporary molar to be full of pus, and absorption of the root and bony crypt, the enamel organ, partially calcified enamel, dentine and the dentine papilla.

The soft tissues have shrunk owing to the action of alcohol



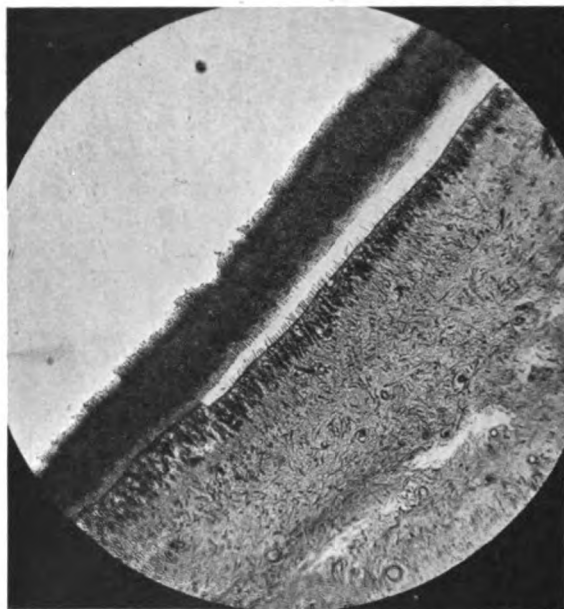


FIG. 8.  $\times 80$ .  
Dentinal processes of odontoblasts. Iron and tannin.

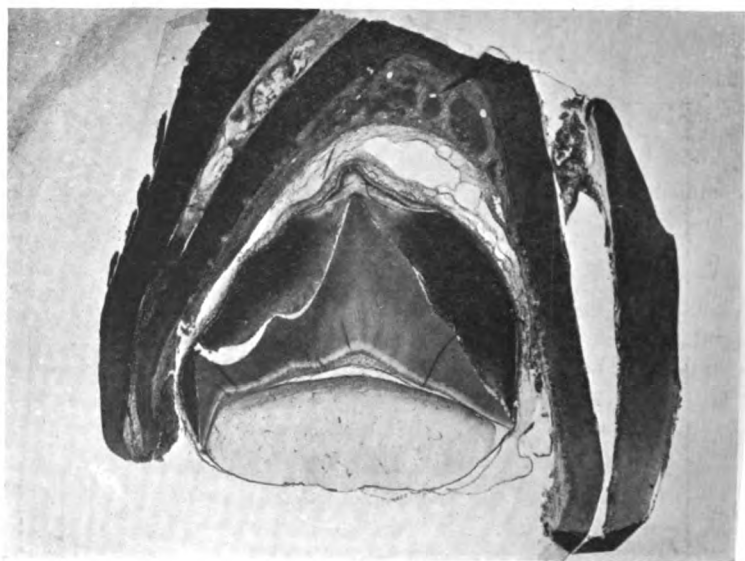


FIG. 9.  $\times 10$ .  
Temporary molar and pre-molar.



and ether, and consequently show a certain amount of distortion.

Another pre-molar extracted in this way was decalcified in 33·7 per cent. formic acid. At the end of forty-eight hours the enamel separated from the dentine in the form of a cap, and I endeavoured to cut sections after embedding in dextrin. The sections so cut were too fragile to handle, and the specimen was therefore embedded in paraffin. Fig. 10 shows the inter-prismatic substance cut transversely and having the well-known honeycomb appearance.

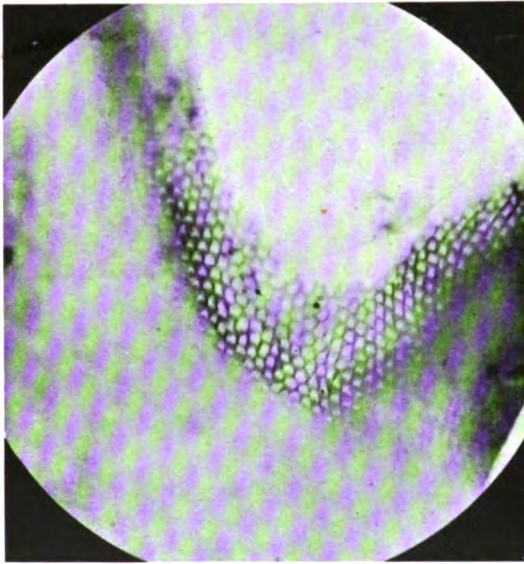


FIG. 10.  $\times 340$ .

Inter-prismatic substance of enamel.

When we come to deal with the attachment of teeth the hake is a good example, since it possesses both ankylosed and hinged teeth. Fig. 11 is a photograph of a tooth of this species, and shows the posterior and the anterior hinge, as figured by Mummery in his recent book. I suggest that the external and internal hinge is a more correct description.

Fig. 12 shows both the ankylosed and hinged tooth, and it will be noticed that the internal hinge appears to be part of the external. This led me to cut some transverse sections of these teeth, and it was then found that the two hinges were one and the same.

Fig. 13 shows that the internal portion is formed by a folding inwards of the external hinge round the pulp, and a longitudinal



FIG. 11.  $\times 15$ .  
Hinged tooth of hake.



FIG. 12.  $\times 15$ .  
Hinged and ankylosed teeth of hake.

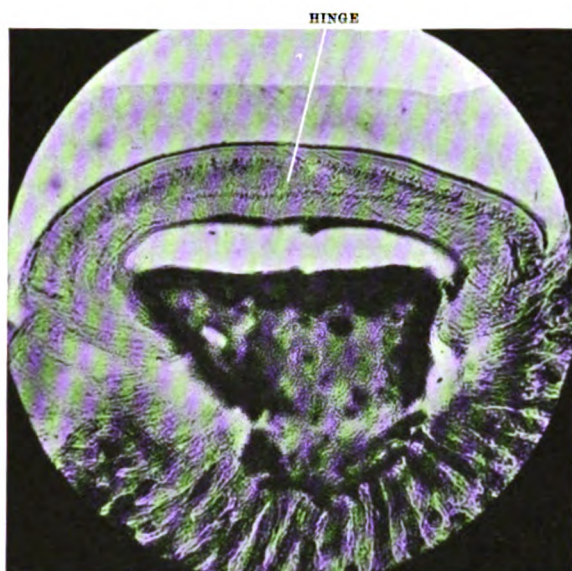


FIG. 13.  $\times 50$ .  
Hinged tooth of hake. Hinge cut transversely.

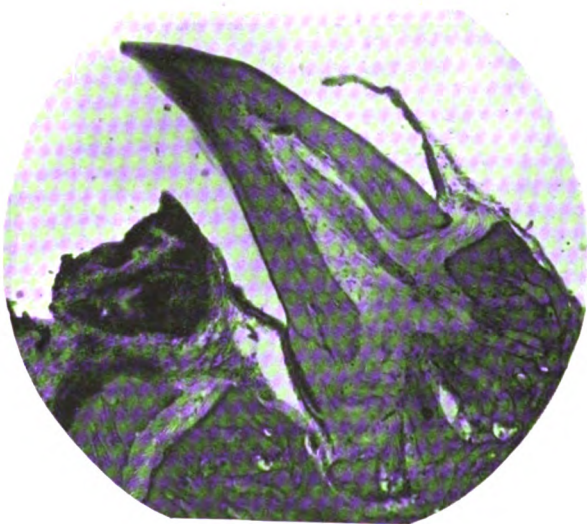


FIG. 14.  $\times 100$ .  
Gill tooth of pike.

section cut towards the outer aspect of the tooth would give the appearance of two separate hinges.

The pike shows a different kind of hinge. It is instructive to study the small gill teeth, which give a good idea of the mechanism, and the larger, such as the vomerine teeth, which give more detail. The former can easily be accommodated in the field of a  $\frac{2}{3}$ rd inch objective, and Fig. 14 is a photograph of such a tooth. Fig. 15, a section of one of the vomerine teeth, shows the elastic fibres attached to prolongations of the osteo-dentine.



FIG. 15.  $\times 85$ .

Vomerine tooth of pike. Elastic fibres attached to osteo-dentine.

Fig. 16 is a photograph from another part of the same section showing their attachment to the bone.

Fig. 17 is from a ground section of one of the large mandibular ankylosed teeth of the pike stained with alcoholic fuchsin. The fine tubes with their still finer branches can be well seen between the coarse osteo-dentine and the enamel.

Fig. 18. In describing the teeth of the eel the text-books do not make much mention of the very definite structure which is interposed between them and the bone. Marett Tims and Hopewell Smith include these teeth among those which are attached by ankylosis, but conclude their description by stating that the actual attachment may perhaps be of a fibrous nature, although a bone of attachment is formed. Mummery places

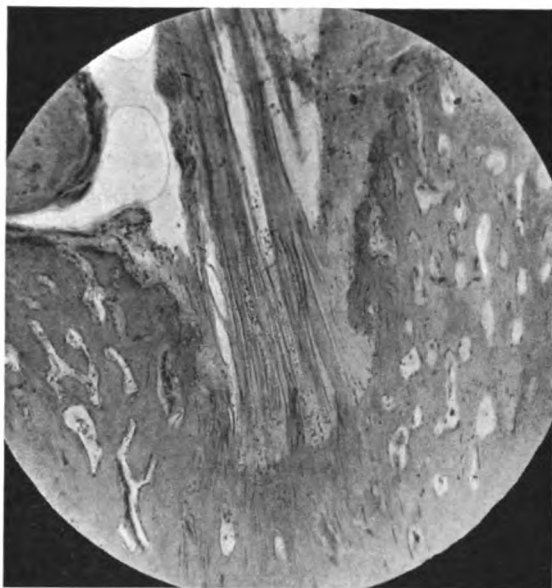


FIG. 16.  $\times 85$ .  
The same, elastic fibres attached to bone.



FIG. 17.  $\times 120$ .  
Ankylosed tooth of pike. Ground section, stained alcoholic fuchsin.



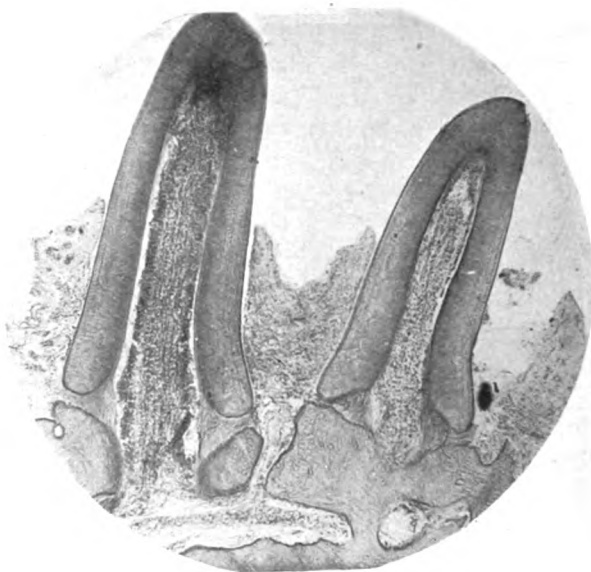


FIG. 18.  $\times 100$ .  
Teeth of river eel showing fibrous attachment.

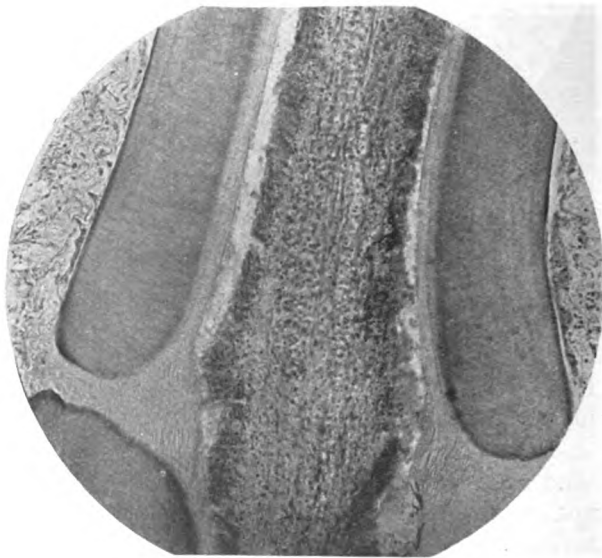


FIG. 19.  $\times 300$ .  
The same.

them among those that have a fibrous attachment, but neither his nor the original illustration by Tomes figure this interposing material. These teeth are attached to the bone by a capsule of fibrous tissue. In those of small fish this is simply interposed between the teeth and the bone. In larger fish, however, this tissue probably extends within the pulp canal for some considerable distance.

Fig. 19 shows the condition still better. It may be mentioned that other sections from the same fish were given out to a class of nearly eighty, and in every case the condition was the same.

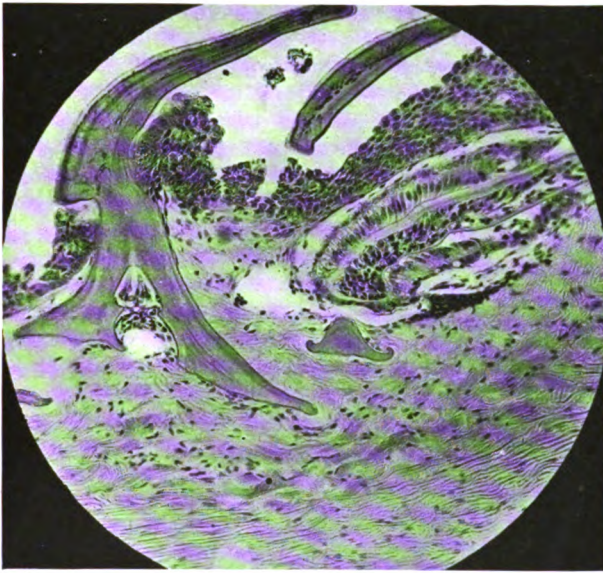


FIG. 20.  $\times 120$ .

Skin of dog-fish. Scale and developing scale.

The dog-fish provides a good example of teeth fixed by means of a fibrous attachment, as well as of the fact that the scales and teeth are identical in structure and in their mode of development. Fig. 20 is from the skin below the mandible, and shows the expanded base of the scale embedded in the fibrous part of the skin. The hard tissues of the scale are composed of osteodentine, and in some cases the fine terminations of the dentinal fibrils appear to penetrate the enamel. The developing scale is also shown and the ameloblasts are very conspicuous.

The teeth of the dog-fish, though larger than the scales, have the same attachment. The structure of the dentine is well shown in Fig. 21, from a tooth in the thecal fold. The large channels

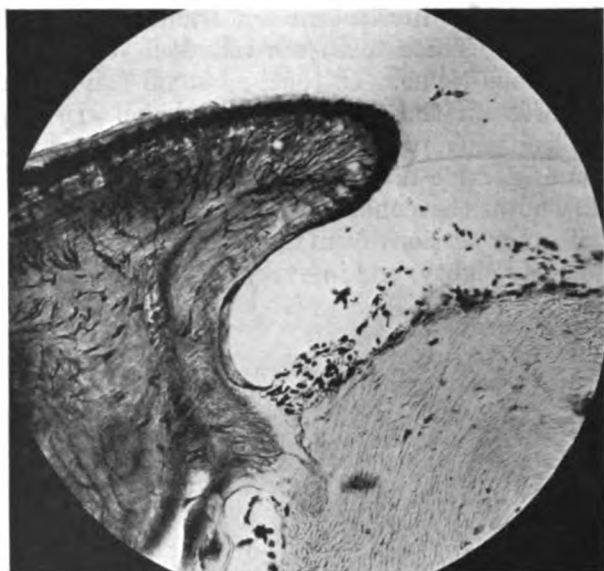


FIG. 21.  $\times 130$ .  
Tooth from thecal fold of dog-fish.

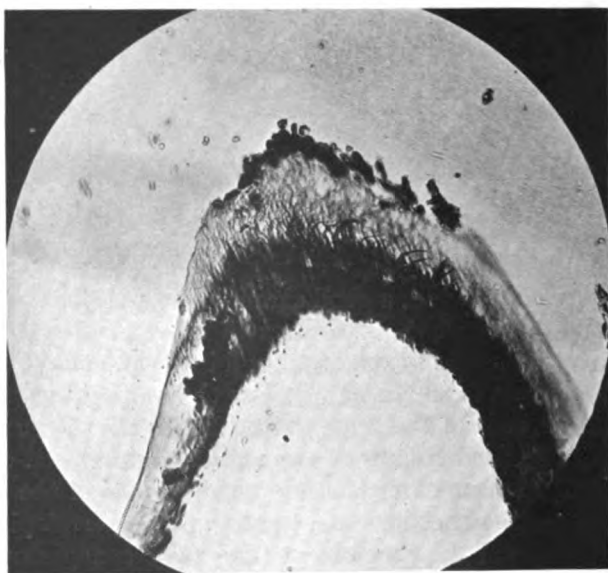


FIG. 22.  $\times 130$ .  
Tooth from thecal fold of dog-fish. Dentine and enamel.



in the dentine are in the main directed towards the periphery of the tooth. The unstained area on the surface is enamel.

Fig. 22 is a photograph of another tooth whose development is incomplete. The enamel is of the tubular variety, and the dentinal tubules can be seen penetrating its substance to the surface.

Fig. 23 is a higher magnification to show the corkscrew appearance of the penetrating tubules.

Fig. 24, *a* and *b*. Passing now to a physiological subject, the absorption of the temporary teeth, it is not difficult, if a good

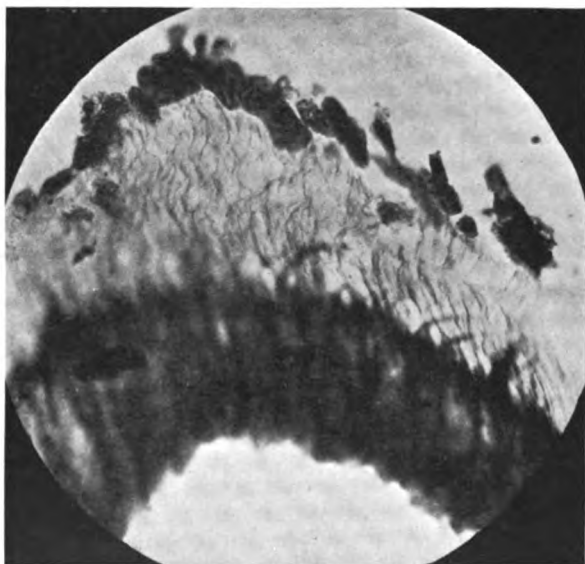


FIG. 23.  $\times 340$ .

The same.

many teeth be cut, to find good examples which show the Howship's lacunæ and the multi-nucleated cells or osteoclasts. At the same time it is extraordinary how often one finds active absorption going on, but no sign of any osteoclasts, and the lacunæ filled up with round cells which form the main part of an absorbent organ.

Fig. 25 is a transverse section of the pulp of a temporary canine, showing osteoclasts.

Fig. 26 is a section of a temporary incisor extracted at the usual time. As it seemed to have a larger absorbent organ than usual, it was hoped it would be a typical example of absorption. It will be seen, however, that it shows epithelium growing underneath the tooth, thus cutting it off from its

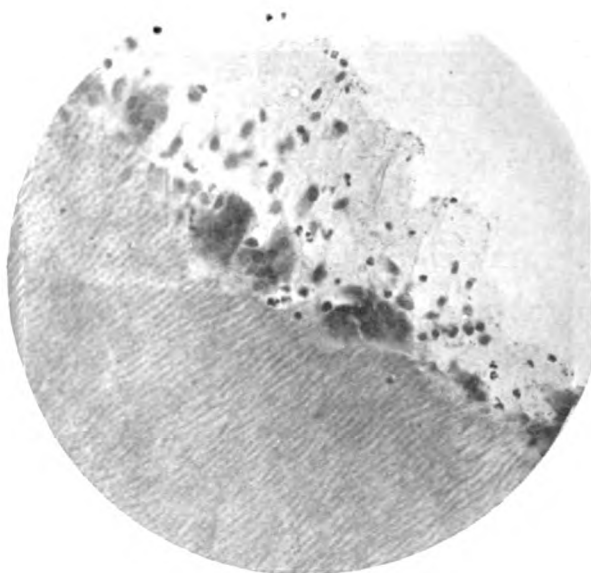


FIG. 24 *a*.       $\times 200$ .  
Osteoclasts. Absorption of temporary tooth.

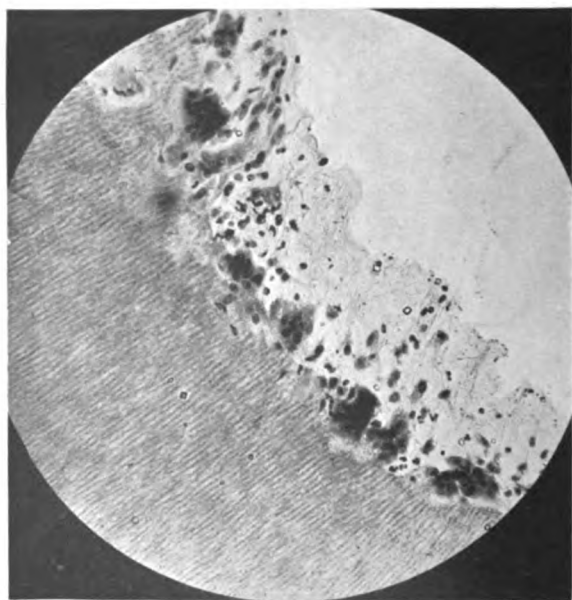


FIG. 24 *b*.       $\times 180$ .  
The same.

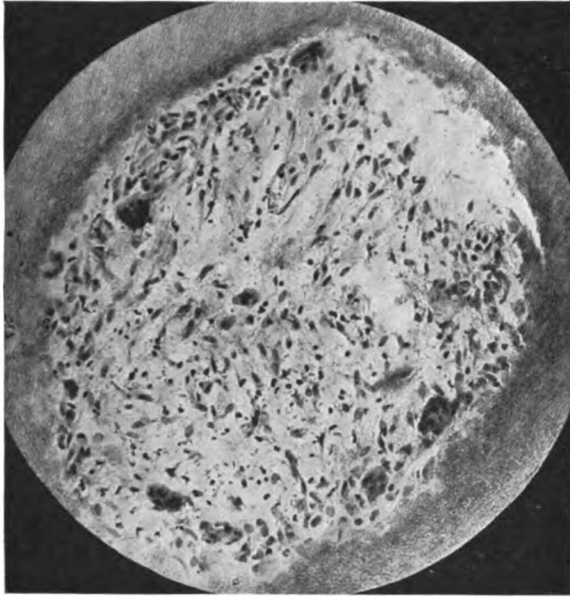


FIG. 25.  $\times 180$ .  
Osteoclasts in pulp of temporary canine.



FIG. 26.  $\times 20$ .  
Temporary canine with epithelium.

attachment. An interesting fact is that the papillæ penetrate in the direction of the tooth and in the opposite one to those of the oral mucous membrane.

Another interesting fact about the temporary teeth is the amount of calcified tissue deposited after absorption has taken place, and evidence of this can be seen in nearly every case.

Fig. 27 is a section of a temporary canine extracted in the ordinary course of events, because the permanent tooth was erupting just above it. For some reason or other the odontoblasts have become active again and have laid down a mass



FIG. 27.  $\times 120$ .

Calco-spherites, osteo-genetic zone. Temporary canine.

of dentine. The appearance of the dentine in this area suggests that this has happened before. This is a useful section, since it demonstrates the appearance of the calco-spherites in recently formed dentine.

Fig. 28 is a section of a temporary canine extracted at the age of sixteen years. It was loose, but the permanent canine was not apparent, although the corresponding tooth on the other side had erupted. There was no pulp canal visible, nor could one be found with the probe. The length of the tooth was 7 mm., and another 2 mm. can be added for loss by attrition. When the sections were examined it was seen that the pulp canal towards the root was completely obliterated, but the

coronal part of the pulp was still in existence and showed slight fibrosis and calcification. The secondary dentine deposited has small canals and irregular spaces in it, and no doubt contained blood vessels which supplied the pulp.

Fig. 29 is a photograph of a temporary canine extracted at the age of sixteen. Although a much shorter tooth, the root being almost completely absorbed, it showed a mass of **secondary dentine** with numerous spaces filling up the coronal part



FIG. 28.  $\times 25$ .

Secondary dentine in retained temporary canine.

of the pulp, and the initial absorption of the dentine is well seen. The character of the deposited tissue in the last two cases is of the hyaline variety, there being very little definite structure in the matrix.

Fig. 30. In a good many cases secondary tissue, having the appearance of cementum, is found. This section of the apical portion of a temporary canine, extracted at the age of twenty-one years, shows very well several masses of secondary cemental tissue.

Fig. 31. A ground section of another retained tooth was

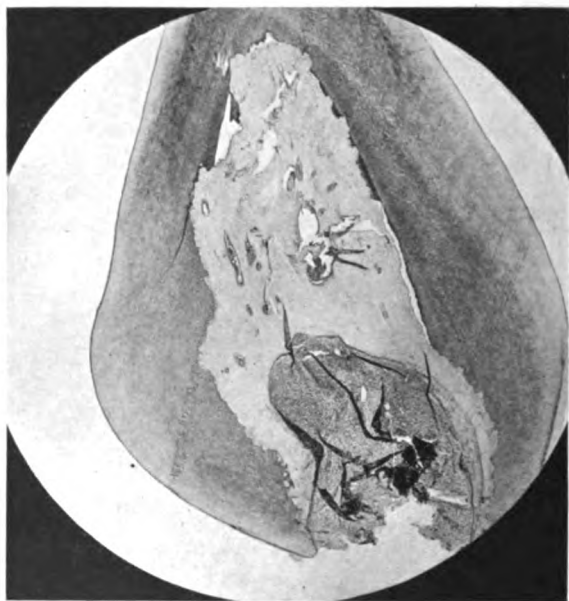


FIG. 29.  $\times 15$ .  
Secondary dentine in coronal part of pulp-chamber. Temporary canine.



FIG. 30.  $\times 15$ .  
Cemental tissue. Apical portion of retained temporary canine.

made as near the centre as possible. The dentine has been absorbed in a very irregular way, and the spaces so left have been filled up with cementum, which shows several larger spaces in addition to lacunæ. The next photograph (Fig. 32) is a higher magnification of A (Fig. 31), and shows one of these larger spaces. The fine processes surrounding it can easily be seen. This space no doubt contained cemental cells which would eventually be cut off to form the contents of lacunæ and canaliculi.

Sections no. 27 to no. 32 show that in the event of a tooth

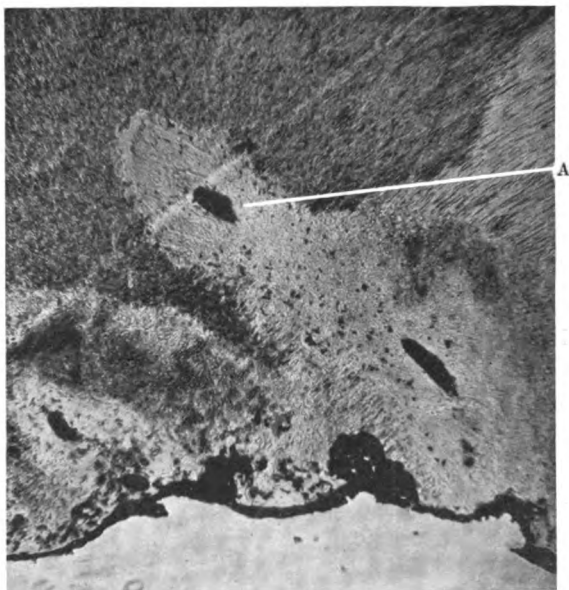


FIG. 31.  $\times 70$ .

Ground section temporary canine. Stained alcoholic fuchsin.

being retained beyond the normal time, the cells of the pulp and periodontal membrane become active, producing new tissue which replaces that lost by absorption.

The next section (Fig. 33) is of a tooth with a somewhat interesting history. A lady aged about twenty-one years came to me complaining of toothache in a left upper temporary canine, which appeared to be quite sound and was firmly implanted in the alveolus. Both lateral incisors were missing, the permanent canines had erupted next to the central incisors, and the right temporary canine was also present but had been filled on several occasions. Her first upper molars had been extracted previously. The patient was definite as to the

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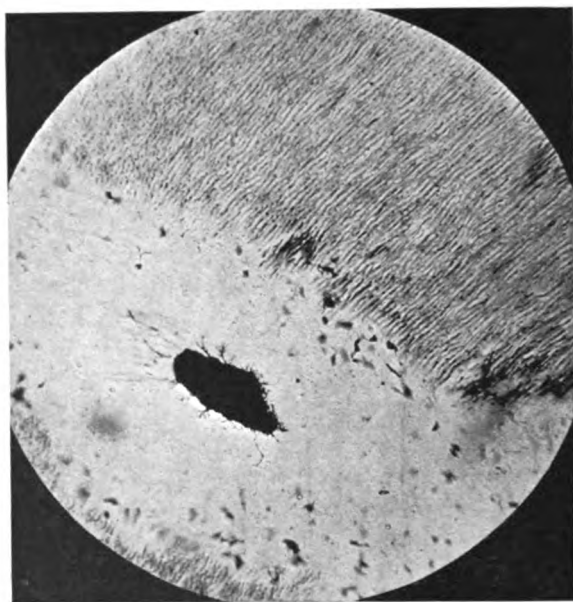


FIG. 32.  $\times 200$ .  
Higher magnification at A (Fig. 31) showing canaliculi.

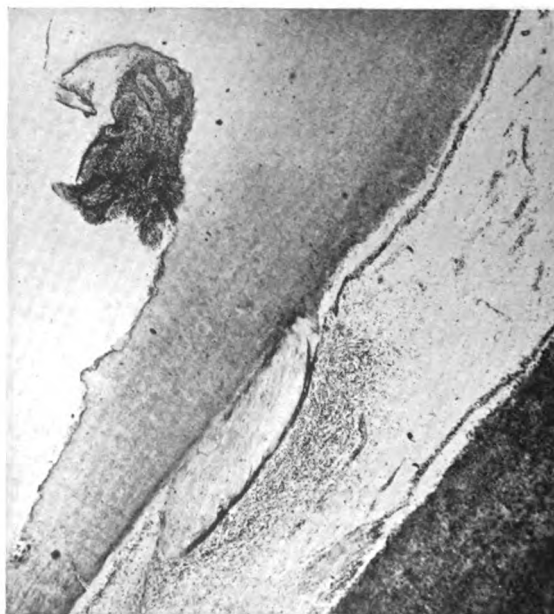


FIG. 33.  $\times 25$ .  
Temporary canine, absorption of root, secondary dentine, pulpitis.



offending tooth, so both temporary canines were extracted. The left temporary canine showed a fairly large zone of absorption, and when sections were cut it was seen that a corresponding area of secondary dentine had been formed in the pulp-canal. The cause of the pain was shown to be pulpitis, and it is possible that infection may have taken place through the thin dentinal wall.

Fig. 34 is a higher magnification of the same section, showing the area of cellular infiltration together with enlarged vessels and their contents.

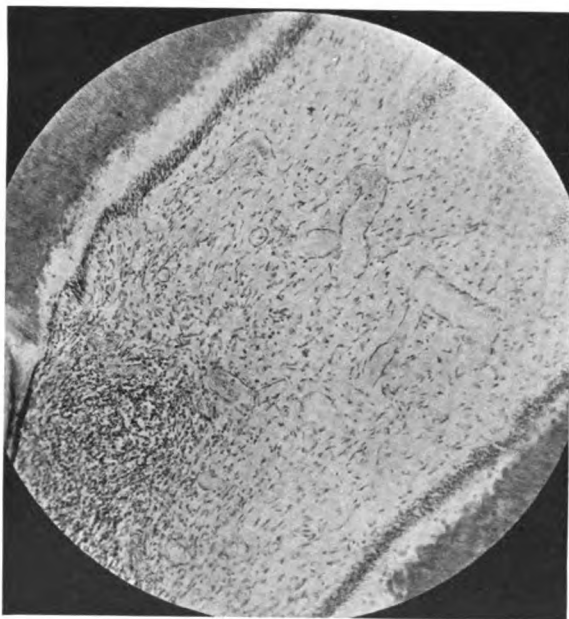


FIG. 34.  $\times 125$ .

The same. Cellular infiltration, enlarged vessels.

Temporary teeth when decalcified often show very definitely the contours of the calco-spherites. In another part of the same section (Fig. 35) these are shown in a striking manner with the dentinal tubules running through them.

Fig. 36 is a photograph of the same specimen, but the tubes have been cut transversely.

The examination of the pulp of teeth extracted in cases of pyorrhœa alveolaris leads one to think that fibroid degeneration is always present to a greater or lesser degree. Lack of time has so far prevented the examination of a definite series of teeth, but one would expect that the pathological lesions

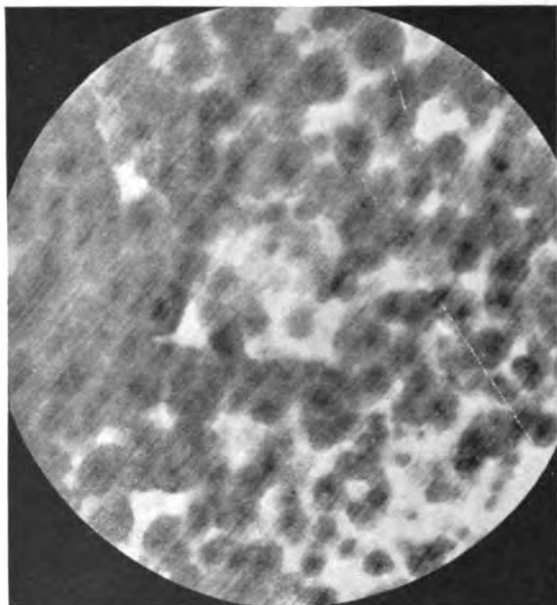


FIG. 35.  $\times 300$ .  
Contours of calco-spherites, dentinal tubules.

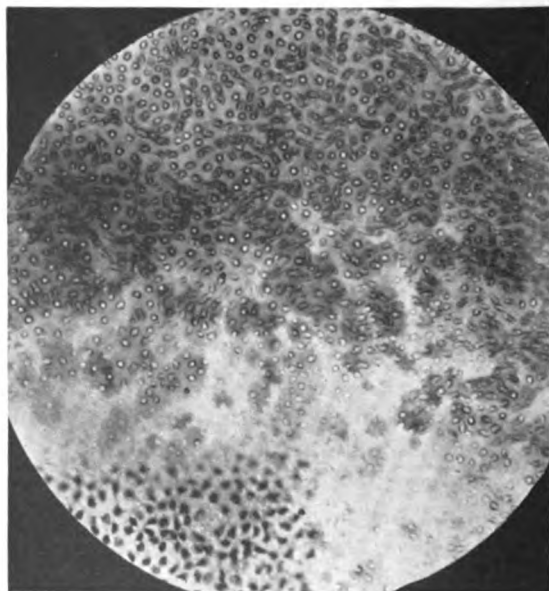


FIG. 36.  $\times 300$ .  
The same. Tubules cut transversely.

of the periodontal membrane and alveolus found in chronic suppurative periodontitis would result in pathological changes in the pulp. Fig. 37 is an early stage of fibroid degeneration of the pulp of a lower pre-molar, extracted because of the somewhat deep pockets. The tooth was not loose, but since the lower incisors had to be extracted on account of the advanced pyorrhœa, it was removed at the same time. The odontoblasts are gathered into sheaves, the vessels are dilated, and there is a marked diminution in the number of cells.



FIG. 37.  $\times 120$ .  
Early fibroid degeneration of pulp.

Fig. 38 is taken from a case of complete fibrosis, the cell element having entirely disappeared.

Fig. 39 is from a case of complete fibrosis which has been preceded by calcification, caused by the presence of a large carious cavity which had been previously filled. The section shows well the fibrous skeleton which remains after the complete degeneration of the odontoblasts, blood vessels and other tissues of the pulp.

A male aged seventeen was seen with reference to an in-standing second upper pre-molar, which was situated in the angle formed by the first pre-molar and the first molar. The second lower pre-molar, which was also in-standing, articulated in the triangle produced by these three teeth. The patient

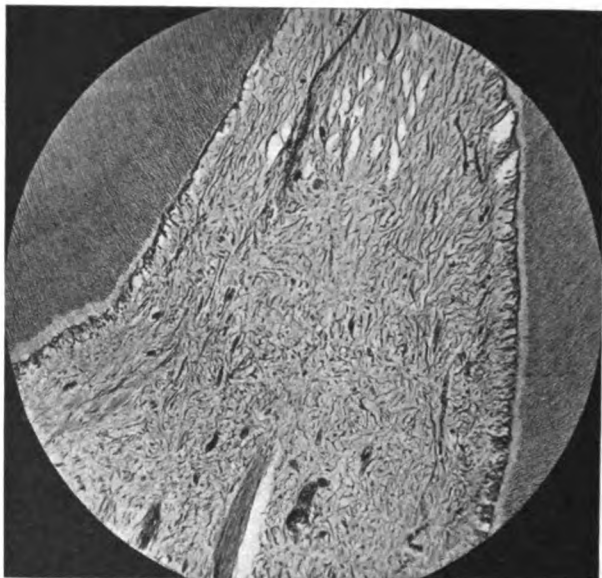


FIG. 38.  $\times 80$ .  
Complete fibroid degeneration of pulp.

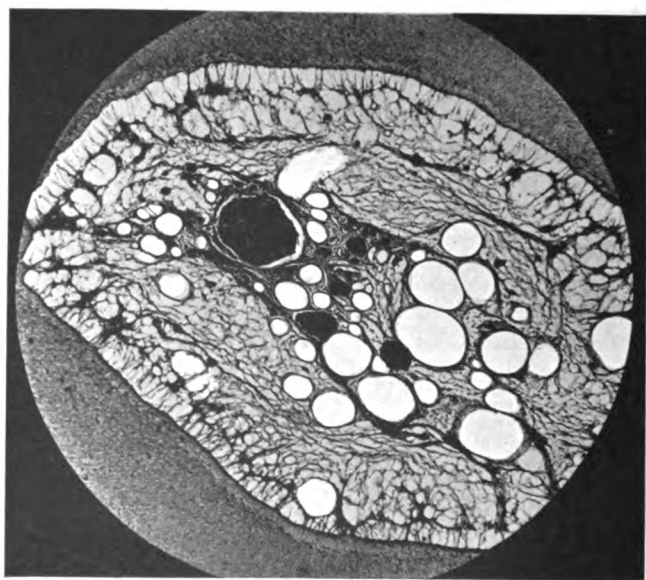


FIG. 39.  $\times 160$ .  
Complete fibroid degeneration and calcific degeneration of pulp.

complained of the amount of food which pocketed into this space and of his inability to clear it even with a toothpick. When his mouth was examined it was very obvious that it would be extremely difficult to remove any material which became impacted between these teeth. The tooth was tender and slightly loose, and the surrounding gum was inflamed. When it was extracted the periodontal membrane was red and inflamed. A small area of absorption about 2 mm. below the enamel margin could be seen with a lens, and the

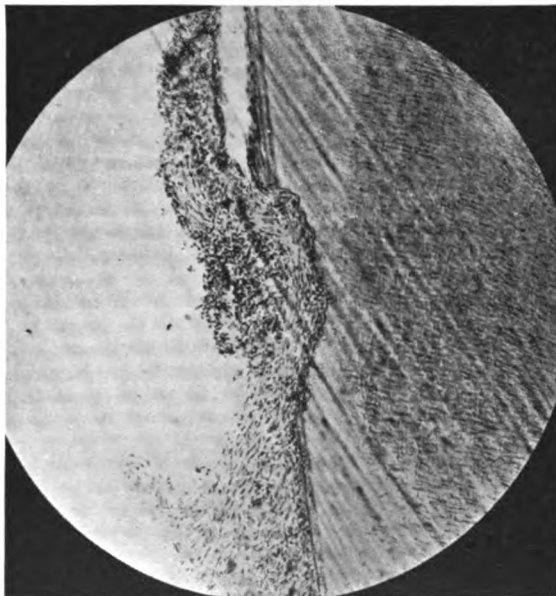


FIG. 40.       $\times 75$ .  
Absorption of cementum and dentine.

apical foramen seemed larger than usual. The tooth was fixed and decalcified in the usual way, sections were cut, and Fig. 40 shows the area of absorption. In other sections it appeared to be a good deal larger.

The pulp was found to be normal, but on each side of the dentine near the apex of the tooth there were areas of hypoplastic cementum. The inflamed periodontal membrane is well shown (Fig. 41).

Fig. 42 shows the apical foramen, and the periodontal membrane can be seen passing round the apex into the pulp. This case is of interest as it shows the results of food impacted between teeth. The injury was severe enough to cause infection



FIG. 41.  $\times 75$ .  
Hypoplastic cementum, inflamed periodontal membrane.

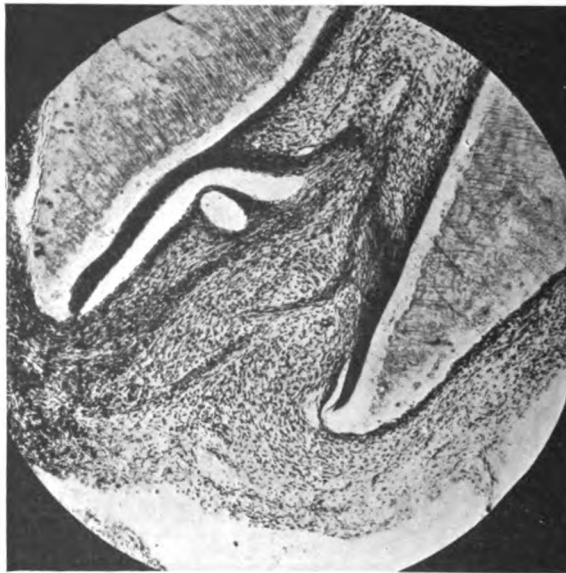


FIG. 42.  $\times 75$ .  
Apical foramen of pulp canal. Periodontal membrane invading pulp.

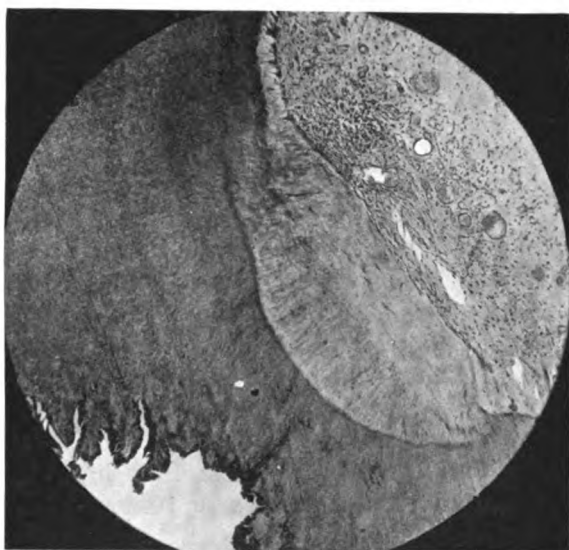


FIG. 43.  $\times 50$ .  
Caries, secondary dentine and pulpitis.

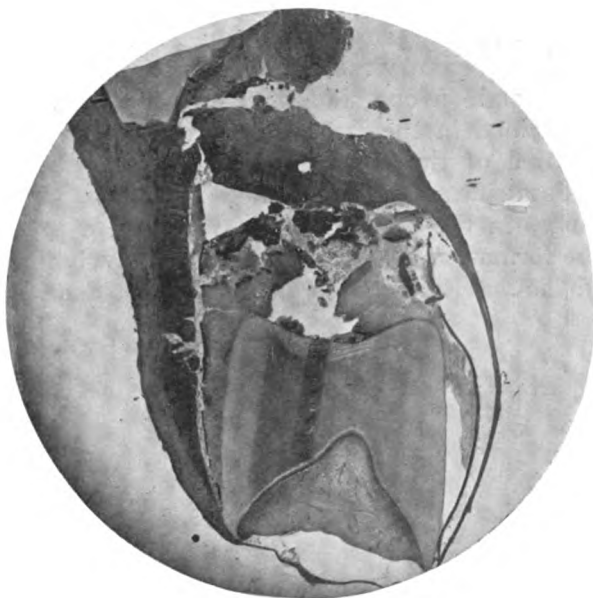


FIG. 44.  $\times 7$ .  
Dentigerous cyst containing pre-molar attached to temporary molar.

of the periodontal membrane, leading to absorption of the cementum and dentine in one area, and hypertrophy of the cementum in another. I suggest that the invasion of the pulp canal by the periodontal membrane was due to the same cause.

Fig. 43 does not need much explanation. It shows a carious cavity with a corresponding area of secondary dentine, and a small area of inflammation showing cellular infiltration and enlarged blood vessels. Sections stained by Gram showed bacterial infection of the tubules in the secondary dentine.

The last section (Fig. 44) is from a specimen of a dentigerous cyst given to me by Mr. Bocquet Bull. It was removed from a girl aged eight, who had a number of carious molars and incisors, and was an everyday type of case. No particular notes were taken beyond the fact that a number of teeth must be extracted. When the first lower temporary molar was extracted there was a soft tumour about 8 mm. in length attached to its root. It was smooth and red. On examination what appeared to be the open apex of a tooth could be seen quite distinctly through the wall of the cyst. The specimen was fixed in 10 per cent. formalin, decalcified in 33·7 per cent. formic acid and mounted in celloidin. Before doing this, some part of the temporary molar was cut away to reduce its size. The photograph shows the cyst attached to the root of the temporary molar. The cyst wall is very much thicker above and on one side than on the other. The premolar is contained in the cyst, which is lined by epithelium, and the enamel of the tooth has been disintegrated in the process of decalcification. It appears from this, that pathological changes in the temporary dentition are a predisposing cause in the formation of dentigerous cysts, involving the premolars and the anterior teeth of the permanent dentition.



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